

**DECLARATION OF NIMISH VAKIL, MD**  
**WITH REFERENCES**

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Pettersson et al

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Serial No.: 10/531,598

Examiner: Micah-Paul Young

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Group Art Unit: 1618

Title: Gastric Acid Secretion Inhibition Composition

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**DECLARATION OF NIMISH VAKIL, M.D., FACP, FACG**

1. I am Nimish Vakil, MD, FACP (Fellow of the American College of Physicians), FACG (Fellow of the American College of Gastroenterology). I am a certified, practicing physician, specializing in internal medicine and, in particular, in gastroenterology. Gastroenterology is a branch of medicine that treats disorders and diseases of the gastrointestinal tract (also called the digestive system).

2. I received my M.D. degree in internal medicine in 1982 from the University of Bombay (Seth G.S. Medical College), Bombay, India. From July 1983 to June 1985, I conducted my residency in internal medicine at New York Medical College Affiliated Hospitals, New York, New York. I received my certification from the American Boards of Internal Medicine in 1985. From July 1985 to June 1987, I conducted my fellowship in Gastroenterology at the Northwestern University School of Medicine, Chicago, Illinois. I received my certification from the American Boards of Gastroenterology in 1987.



3. Besides being a certified physician who has treated patients since 1985, I have been a professor of medicine on the faculties of the University of Texas, Austin, Texas (Assistant Professor: 1987-1988); University of Rochester, Rochester, New York (Assistant Professor: 1988-1993); University of Wisconsin, Madison, Wisconsin (Clinical Associate Medicine: 1993-1997); University of Wisconsin Medical School, Madison, Wisconsin (Clinical Professor of Medicine: 1997 to the present); and the Marquette University College of Health Sciences, Milwaukee, Wisconsin (Clinical Associate Professor of Medicine: 2002 to the present) (dual appointment with the University of Wisconsin Medical School).
4. I attach my Curriculum Vitae (CV) (Attachment 1). My CV recounts my educational and professional experience and associations. My CV also lists my many peer-reviewed publications; book chapters; invited papers/editorial; and national and international professional assignments in the field of internal medicine and gastroenterology, which well exceed 200 in number. Recently, I have been honored by an official invitation to author a key chapter on peptic ulcer disease for the upcoming 9<sup>th</sup> Edition of Schlesinger and Fordtran's *Gastrointestinal and Liver Disease (Pathophysiology/Diagnosis/Management)*, which is the leading textbook (the professional "bible") in the field of gastroenterology.
5. An area of personal and professional interest, experience, and expertise for me as a physician and educator within the field of gastroenterology is in the treatment of the disease called gastro-esophageal reflux disease (GERD). I have studied the medical literature and myself written extensively on the subject, having, since 2000, authored or co-authored over 30 publications directed to the pathophysiology, diagnosis, and management of GERD (these are listed in my CV).
6. My personal and professional interest, experience, and expertise in this area are recognized by my colleagues. For example, in 2002, I was among twenty-eight

participants from ten countries who were selected on the basis of their interest, experience, and expertise in the treatment of GERD. We met in Marrakesh, Morocco during a two day international multidisciplinary workshop to critically review the data regarding the reliability, processes, and priorities for symptom evaluation in GERD patients. (see Dent, Armstrong, Delany, Moayyedi, Talley, Vakil, "Symptom Evaluation in Reflux Disease: Workshop Background, Processes, Terminology, Recommendations, and Discussion Outputs," *Gut* 2004; 53 (Suppl IV):iv1-iv24) (Attachment 12) . In 2002, I was also honored by the selection as chairman of an international consensus group of experts and family physicians selected on the basis of their "demonstrated knowledge/expertise in GERD by publication/research or participation in national or regional GERD consensus guidelines or an interest in guideline development and dissemination." Our aim was to develop the first ever global consensus definition of GERD (which came to be known as the "Montreal Definition") that could be used clinically by primary care physicians and that embraced the needs of physicians, patients, researchers, and regulatory bodies from different parts of the world. (see Vakil et al, "The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus," *Am J Gastroenterology* 2006: 101:1900-1920 (Attachment 13); Flock, Jones, and Vakil, "Approach to Gastroesophageal Reflux Disease in Primary Care," *Can Fam Physician* 2008; 54:701-5) (Attachment 14). I was recently honored to be included among a faculty panel of eight physicians in a recent continuing medical education program sponsored by the American Gastroenterological Association to address "Improving the Management of GERD: Evidence-Based Therapeutic Strategies," supported by an unrestricted educational grant from Johnson & Johnson Merck Consumer Pharmaceuticals Co. I and my fellow panel members were identified as "practicing experts devoted to the investigation of and treatment of GERD and GERD-related illness."

7. Due to my interest, experience, and expertise as a physician and educator in the field of gastroenterological disorders, I am asked to provide research support for companies who conduct research and development in the pharmacology field.

Companies that I have provided research support for include AstraZeneca; Novartis; Boston Scientific; Medtronic; Altana; XenoPort; AGI. Due to my experience and expertise as a physician and educator in the field of gastroenterological disorders, I am also asked from time to time to consult with companies in the pharmacology field, including AstraZeneca; Merck & Co.; Pfizer Limited; Axcan; Orexo; Novartis; Shire; TAP Pharmaceutical Products, Inc.; Janssen Pharmaceutica; Procter and Gamble; XenoPort; Ortho-McNeil; Meridian; and GlaxoSmithKline. In the interest of full disclosure, I also report that I personally own a small number of shares in the publically traded companies of Orexo and Meridian.

8. I have been asked to comment about the discovery made Anders Pettersson, M.D., and his colleagues at Orexo in 2001-2002 of a method for the on demand treatment of symptoms of gastro-esophageal reflux disease (GERD), of which I am personally familiar and have studied. The method co-administers in an oral dosage form a proton pump inhibitor or a salt thereof (PPI) and an H2 receptor antagonist or a salt thereof (H2RA). The PPI is coated, whereas the H2RA is not, to delay and/or extend the release of the PPI relative to the release of the H2RA in the gastro-intestinal tract. The oral dosage form is administered on demand -- that is, when a patient experiences a GERD symptom -- to deliver into the gastro-intestinal tract a dosage amount of the PPI (coated) simultaneously or concomitantly with a dosage amount of the H2RA (not coated). The co-administration of the coated PPI and the uncoated H2RA affects a rise of gastric pH to above about 3 within about 2 hours of the administration. This dosage regime permits a repeat of the oral administration just described, on demand -- based upon a subsequent occurrence of a GERD symptom-- if necessary, over a prolonged period. In shorthand, I will refer to this discovery by Dr. Pettersson and his colleagues as the "Invention."

9. I understand that the Invention is the subject of pending United States Patent Applications. I also understand that the United States Patent Office has taken the position to the effect that one of ordinary skill in the art would have been motivated by the teachings and suggestions of the published literature on the subject of treating GERD

with H2RA's or PPI's, to combine a H2RA and PPI in a single dose form for co-administration. I respectfully challenge this assessment, because it is inconsistent with what my colleagues and I in the field believed at a time prior to the Invention. The published literature on the subject of treating GERD did not teach the co-administration of H2RA with PPI. In fact, I believe the opposite is true. I believe the Invention is novel and not suggested by the prior published literature, and I will explain why.

10. I will comment about the Invention from the perspective of a person who has spent over twenty years in the field of gastroenterology and related pharmacology. As the above summary of my background indicates, I am a person who has considerable interest, experience, and expertise in the physiology of gastric secretion in the human stomach, the physiology of GERD, and the pharmacology of the drugs that have been used to treat the disease in the years prior to the Invention. As a professor, I teach others in these matters at medical schools. As a medical doctor, I have myself authored many peer-reviewed articles on these matters, and I have read many peer-reviewed articles and textbooks written by my colleagues. I regularly attend (and I am honored to sometimes chair) professional conferences where these matters are openly discussed and debated among my fellow doctors and scientists. This is the way professionals in my field share our scientific and clinical interests, experiences, and expertise pertaining to GERD and its treatment. I think these traits characterize professionals like me and my colleagues who practice in the field of gastroenterology and related pharmacology, so when I speak for myself, I am speaking for my colleagues in general.

11. When I first learned about the Invention, I was skeptical about its scientific and medical efficacy. From the perspective of my background, expertise, and experience at the time, the co-administration of H2RA and PPI simultaneously or concomitantly made no scientific or pharmacological sense to me. To me and others in my field, the co-administration of H2RA and PPI simultaneously or concomitantly was at that time scientifically and clinically illogical, and it could also be a disservice to a human patient. I will in this Declaration explain why my colleagues and I thought this way, because it is

important to gain an understanding and appreciation of our view of the nature of the Invention.

12. I have studied the scientific and clinical efficacy of the Invention. It is my opinion now that the Invention qualifies as a scientific and clinical "breakthrough" in the sense that it changes the way that my colleagues and I in the field had, prior to the Invention, thought about the pharmacology of drugs like H2RA's and PPI's and their physiologic effects on acid secretion in the stomach in the treatment of GERD. Before the Invention, my colleagues and I believed that it was never appropriate to co-administer a H2RA and PPI simultaneously or concomitantly. Further, at that time, my colleagues and I were confident that we had the requisite logical, scientific, and medical reasons to back-up our beliefs in this respect. The Invention has challenged us to rethink our beliefs on the subject.

13. To appreciate our view of the Invention, one must look through the eyes of a person like me, at a time prior to the Invention, to understand how at the time we treated GERD (as I will describe in greater detail in paragraphs 14 to 26 *infra*), and to understand what my colleagues and I believed at the time about the biochemical cellular mechanism which generates and secretes gastric acid in the stomach (as I will describe in greater detail in paragraphs 27 to 34 *infra*), and to understand what we at that time believed H2RA's did to interrupt this mechanism in the treatment of GERD (as I will describe in greater detail in paragraph 35 *infra*), and to understand what we at that time believed at that time PPI's did to interrupt this mechanism in the treatment of GERD (as I will describe in greater detail in paragraphs 36 and 37 *infra*) -- and then one will understand why, at the time, the co-administration of H2RA and PPI simultaneously or concomitantly in the treatment of GERD made no scientific sense to us, and why we believed it could be a disservice to humans (as I will describe in greater detail in paragraphs 38 to 43 *infra*).

14. As a physician, I am professionally and ethically motivated to identify and use the best available treatment options for dealing with the symptoms of GERD. I have studied and written about these symptoms and the profound effects that they have on the quality of life of people with GERD (see American Journal of Gastroenterology, Vol. 96, No. 2, 2001. pp. 303-314, accepted for publication October 6, 2000) (Attachment 2). I have written: "In general, patients with GERD experience more pain and greater impairment in social functioning and emotional well-being than patients with other chronic diseases such as diabetes and hypertension." I have also written: "Successful treatment led to marked improvement in the quality of life." (p.309).

15. I have also studied and written about the pharmacological treatment options that were available to me to treat my GERD patients in 2000. These included (i) antacids; (ii) H2RA's; and (iii) PPI's. (see American Journal of Gastroenterology, Vol. 96, No. 2, 2001. pp. 309) (Attachment 2). My colleagues and I in the field knew at that time (and today) that antacids, H2RA's, and PPI's are distinctively different pharmaceutical agents. They work in distinctively different ways. An antacid is, by legal and scientific definition, not an H2RA or a PPI, and vice versa.

16. Antacids are merely weak bases -- such as sodium bicarbonate, magnesium hydroxide, or aluminum hydroxide (Rolaids® or TUMS®) -- that chemically react with gastric acid in the stomach after it is secreted (illustrated in Figure 10 *infra*). What constitutes (and, conversely what does not constitute) an antacid was well known and identified at that time, both chemically and legally by the FDA. Substances that were recognized by persons of skill in the art at that time to be antacids were listed in Title 21 U.S.C. § 331.11 (Food and Drugs) (1974) (Attachment 3). Antacids do control the effects of gastric acid by neutralization, but for a very short period of time. Some studies show that they last twenty to twenty-five minutes, and then lose their effectiveness. These are not practical except for the occasional symptom of heartburn, but then you have to carry a bottle of Rolaids® or TUMS® with you, and you still have heartburn.

17. H2RA's and PPI's on the other hand are so-called "anti-secretory" agents, which act by preventing the secretion of gastric acid in the first place. Both classes of drug are absorbed by the small intestines and circulated by blood to parietal cells in the stomach, where they exert their effect at a cellular level. As explained in more details in paragraph 35 *infra*, H2RA's block the action of histamine in parietal cells. They were the first class of anti-secretory drugs to appear in the clinic (in the 1970's) and include cimetidine (Tagamet®), ranitidine (Zantac®) and famotidine (Pepcid®). PPI's emerged a decade later and act by irreversibly binding to the H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme (the proton pump), as explained in more detail in paragraphs 36 and 37 *infra*. Such drugs, which include omeprazole (Prilosec®), esomeprazole (Nexium®) and lansoprazole (Prevacid®), proved to be more potent inhibitors of gastric acid secretion than H2RA's.

18. In 2000, I reviewed the treatment strategies involving H2RA's and PPI's as reported in the medical literature prior to 2000 (see N. Vakil, "Review Article: Cost-Effectiveness of Different GERD Management Strategies," *Aliment Pharmacol Ther* 2002; 16 (Suppl. 4): 79-82, p. 80) (Attachment 4). In this article, I concluded at that time, based upon my review: "Proton pump inhibitor therapy is more effective than H2 receptor antagonist therapy in erosive GERD." (p. 80). The shortcomings of H2RA therapy in treating GERD were well known and recognized in 2000. The H2 Receptor on a parietal cell is prone to feedback on itself. The more you block a receptor, the more the cell will respond to that by developing a tolerance to the agent that it is exposed to, so it will find a way to bypass the process. The H2 receptors are in this respect quite prone to tolerance, and the treatment effect decreases with time. In the article I co-authored in 2000 with Ronnie Fass, M.D., and M. Brian Fennert, M.D., we reported a 1999 study in which symptomatic GERD patients with an incomplete response to a three month therapy with a twice daily dose of H2RA, were subject to a further two months of continued therapy at a double dose of H2RA with only modest improvements compared to controls, leading us to note the "pharmacological deficiencies of H2RA's in controlling acid secretions" (see *American Journal of Gastroenterology*, *Ibid*, p. 309) (Attachment 2). In the same article, we further commented: "[H2RA] agents have been known to be

ineffective in inhibiting meal-stimulated acid secretion and are associated with rapid development of pharmacological tolerance" (Ibid). We also cite data that "indicate overwhelmingly that, in patients with erosive esophagitis, PPI's provide superior healing and symptom relief compared to H2RA's ..." (Ibid, p. 309-310). In my review article (*Aliment Pharmacol Ther* 2002; 16 (Suppl. 4): 79-82, p. 80) (Attachment 4), I described a "step-up" therapy option (disclosed in an earlier peer-reviewed article in 1999) that begins with a generic H2RA therapy. Failures with this strategy (as tolerance develops) would be treated with a higher dose of H2RA therapy, and failures to the higher dose H2RA are then treated (stepped up) with PPI therapy. There was also a corresponding "step down" therapy, in which you start with PPI's, make the patient feel better, and then step down to the less expensive H2RA's. There were reports also of a therapy option for what was called "nocturnal reflux" (in which GERD patients already on PPI therapy experience intragastric pH less than four at night), in which PPI's were administered with the morning meal and the evening meal and H2RA's were separately administered later at bedtime, although there was little data at the time that demonstrated the long term efficacy of this approach, as tolerance to the H2RA's would build (Vakil, "Novel Methods of Using Proton-Pump Inhibitors," *Gastroenterol Clin N Am* 31 (2002) S85-88, 87-88) (Attachment 5). Similarly, in a clinical study we evaluated the efficacy of H2RA's separately administered at bedtime to prevent nocturnal heartburn and demonstrated that tolerance to the effects of H2RA's develops when they are used beyond seven days. (Vakil et al., "The Effect of Over-the-Counter Rantidine 75 mg on Night-Time Heartburn in Patients With Erosive Oesophagitis on Daily Proton Pump Inhibitor Maintenance Therapy," *Aliment Pharmacol Ther* 23 (2006), 649-653 ) (Attachment 11).

19. PPI's, though superior to H2RA's in treating GERD, had their clinical shortcomings, too. First and foremost, there was a significant time lag (4 days) between the administration of PPI and the relief of the symptom. This was because the PPI's are prodrugs that are administered in an inactive state and need to be subjected to the acid environment of a stimulated parietal cell to become activated by chemical conversion to a active entity that blocks the proton pump. This is discussed in more detail in paragraphs



39 and 40 *infra*. The chemical conversion that occurs in the parietal cell is illustrated in Figure 4 of a peer-reviewed article on this subject at the time written by colleagues in the field, M. Michael Wolfe, M.D. (Professor, Boston University School of Medicine) and George Sachs, M.D. (Professor, UCLA School of Medicine), "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome," *Gastroenterology* 2000; 118:S9-S31 (Attachment 6).

20. Thus, with PPI therapy, it took time before sufficient proton pumps were inhibited for the patient to feel an effect. In contrast, H2RA therapy provided rapid relief, but it faded with time. With PPI's, prompt relief was not possible, even at higher dosage levels, so the profound debilitating effects of GERD could not be promptly moderated, but came only with the passage of time.

21. In 2000 therefore, we physicians dedicated to the treatment of the symptoms of GERD had imperfect pharmacological tools at their disposal. The therapeutic tools that were available to us left the problem of rapid and prolonged relief from the symptoms of GERD unsolved. The conventional wisdom expressed in the leading medical textbooks and held by the thought leaders in the field at this time advocated (i) H2RA therapy or (ii) PPI therapy or (i) H2RA therapy then (ii) PPI therapy, or *vice versa*. H2RA's provided prompt relief but their effect faded with time. This caused increasing doses of the H2RA's to be used until the therapy ultimately failed. Ultimately, the symptoms GERD persisted to disrupt the patient's quality of life. With PPI's, you had to accept a significant time lag of several days, during which the patient continued to suffer the profound quality of life effects. The problem of having no therapy that made possible rapid and prolonged relief from the symptoms of GERD persisted in 2000 and is evidenced in published literature of the time, as reflected in my publications and the publications of other persons of skill in the gastroenterology field.

22. Importantly, at a time prior to the Invention, my colleagues and I were faced with pointed teachings in the peer-reviewed literature not to co-administer a H2RA with a PPI together simultaneously or concomitantly in humans. To us, the teachings against co-administration of H2RA's and PPI's in humans made scientific and pharmacologic sense, and it was also backed by animal data that suggested that such a combination would not work. At a time prior to the Invention, I would not even have considered co-administering H2RA's and PPI's together simultaneously or concomitantly to human subjects by virtue of both the lack of scientific rationale and adverse dog data. In view of this, we used to teach medical students not to co-administer H2RA's and PPI's concomitantly or simultaneously.

23. To illustrate this point, the leading medical textbook in the field of gastroenterology (at the time and now; see 6<sup>th</sup> Edition of Schlesinger and Fordtran's *Gastrointestinal and Liver Disease (Pathophysiology/Diagnosis/Management)* (1998) (Attachment 7)) accurately reflects the scientific, clinical, and pharmacological state of mind of experts at the time. In the chapter concerning "Peptic Ulcer and Its Complications," a colleague in the field Andrew H. Soll, M.D. (Professor of Medicine, University of California) makes this scientific and clinical observation about PPI's and H2RA's:

*"PPI's effectively inhibit only stimulated parietal cells. Because PPI's must be concentrated and activated in the acid compartments of the parietal cells, they will only inactivate the H<sup>+</sup>,K<sup>+</sup> -ATPase present in actively secreting membrane compartments. PPI effectiveness therefore depends on the degree of activation of acid secretion at the time of drug administration."* (at page 649).

Dr. Soll further counsels physicians, like me, who are interested in providing prompter relief to their GERD patients:

“Combination therapy [of PPIs] with H2RAs is never appropriate; if greater antisecretory efficacy is required, the PPI should be administered in higher, divided doses.” (at p. 649).

24. In the preceding 5<sup>th</sup> Edition (1993) of the same textbook (on pages 626-627) (Attachment 8), Dr. Soll provides the same teachings. This demonstrates that the proscription against co-administration was well established in the field prior to the Invention:

“THE PARIETAL CELL HAS TO BE TURNED ON TO BE TURNED OFF BY OMEPRAZOLE [a PPI]. Since omeprazole must be concentrated and activated in the acidic compartments of the parietal cell, omeprazole will inactivate only the H<sup>+</sup>, K<sup>+</sup> - ATPase present in actively secreting membrane compartments.” (at page 626).

“A FEW PRACTICAL POINTS. ... Omeprazole should not be co-administered with another antisecretory agent.” (at page 627).

In both sections authored by Dr. Soll in the 5<sup>th</sup> and 6<sup>th</sup> Textbook Editions point to experiments on dogs which showed that the co-administration of H2RA's and PPI's caused a profound, undesirable effect.

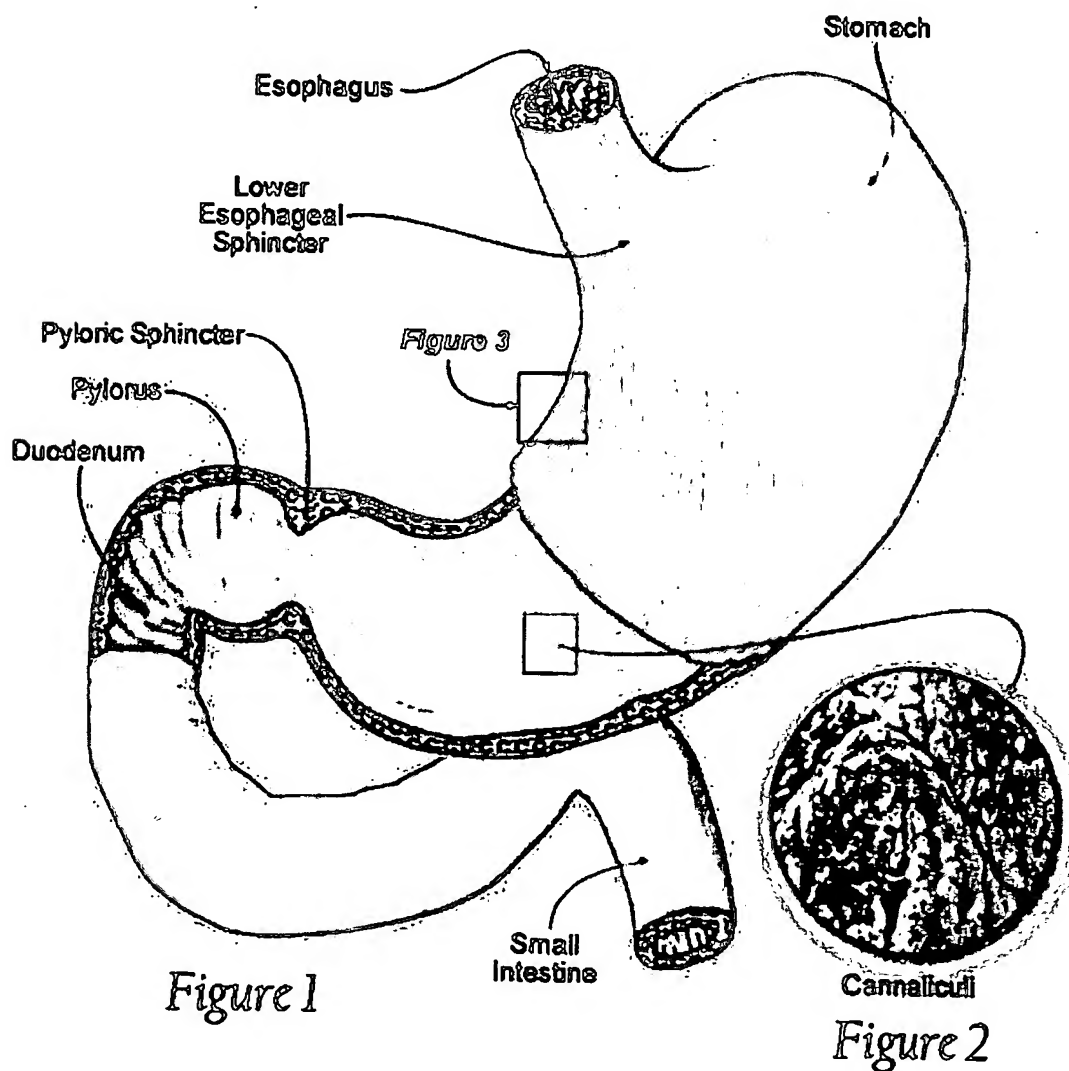
25. I also quote from another peer-reviewed article on this subject at the time written by colleagues in the field, M. Michael Wolfe, M.D. (Professor, Boston University School of Medicine) and George Sachs, M.D. (Professor, UCLA School of Medicine), “Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome,” *Gastroenterology* 2000; 118:S9-S31 at S14 (Attachment 6) (the emphasis appears in the authors' original text):

“The PPIs are without question the most potent inhibitors of gastric acid secretion available. However, because they are most effective when the parietal cells is stimulated

to secrete acid in response to a meal, these drugs should *only* be taken before or with a meal and should *not* be used in conjunction with H2-receptor antagonists, postaglandins, or other antisecretory agents (see Table 3)” Table 3 (Helpful Facts on the Use of PPIs) further states: “Do *not* administer [PPIs] concomitantly with H2-receptor antagonists or postaglandins.”

26. The teachings against co-administration of H2RA's and PPI's simultaneously or concomitantly in humans found in the leading peer-reviewed literature at that time were founded upon the consensus scientific and clinical knowledge about the physiology of gastric secretion in the human stomach and the pharmacology of H2RA and PPI in that environment. I will explain this with reference to a series of illustrations that have been prepared to help exemplify my explanation.

27. Figure 1 illustrates by way of general introduction a human stomach and the unique cells, called parietal cells, which line the stomach lumen. These are the parietal cells that the foregoing articles describe. Parietal cells secrete hydrogen  $H^+$  ions (protons) in the form of concentrated gastric (hydrochloric) acid from invaginations that line the stomach, called canaliculi. Only parietal cells perform this function in humans. By way of further introduction, Figure 2 illustrates what these canaliculi look like when viewed through a scanning electron microscope. There are about one billion parietal cells in a human stomach.



28. Figure 3 is a diagrammatic representation of the anatomic and biochemical components of a parietal cell. A series of biochemical steps occur within a parietal cell that lead to the formation and secretion of gastric acid.

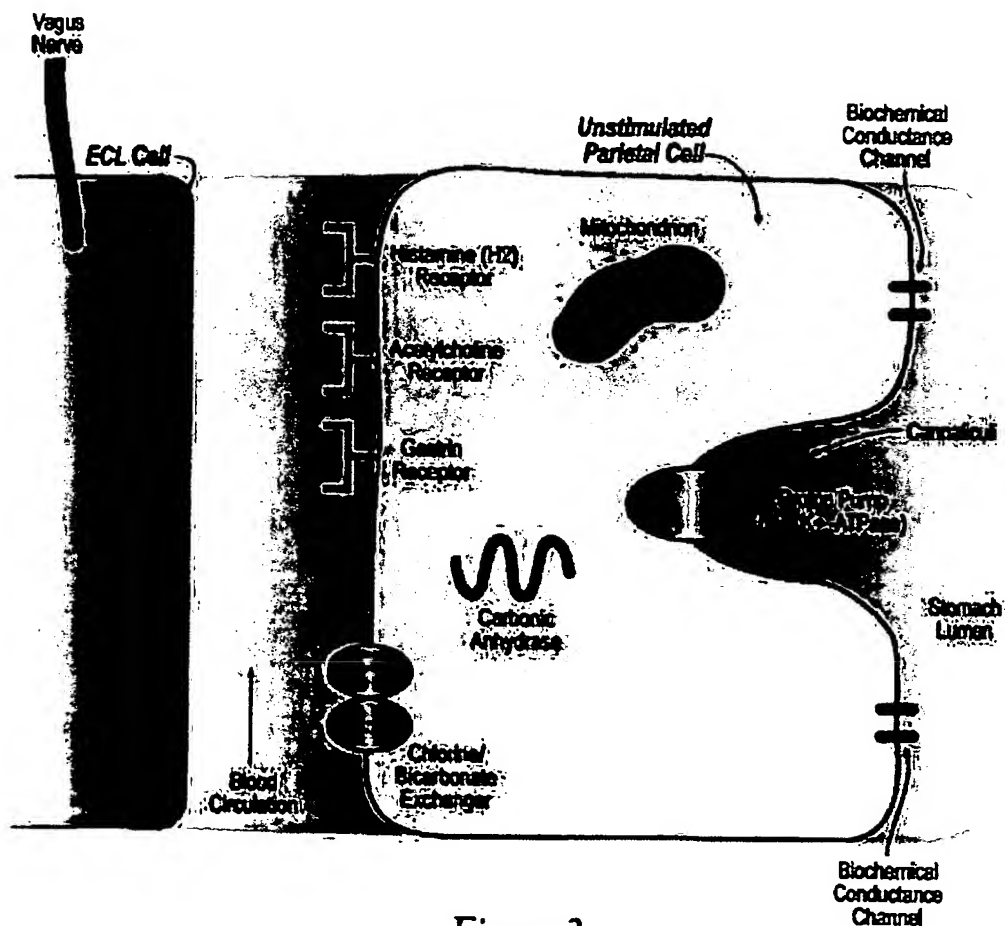


Figure 3

29. The beginning point of the reactions occurs when the parietal cell is stimulated. Figure 3 diagrammatically illustrates the specialized receptors of the parietal cells, where the stimulation occurs. The receptors have specific chemical affinities for particular organic molecules that circulate in the blood. One of these receptors, the H2 Receptor, has an affinity for histamine.

30. Histamine is released into the blood by specialized cells in the stomach (called ECL cells) when stimulated by the vagus nerve in response to a person's sight and smell of food and the act of eating (as Figure 4 illustrates). When the histamine carried in the blood binds with H2 Receptor (as Figure 5 illustrates), the parietal cell is stimulated. The chain of cellular actions ultimately leads to the secretion of gastric acid.

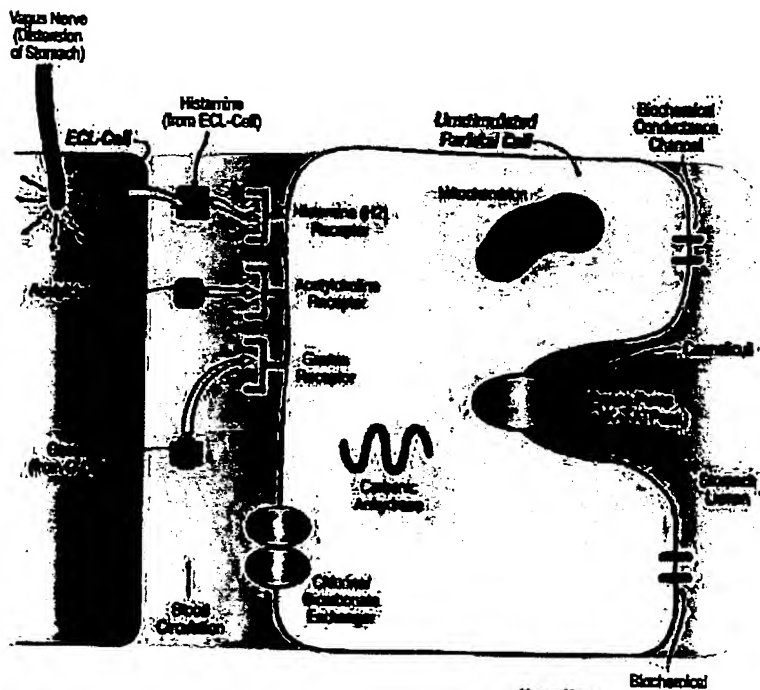


Figure 4

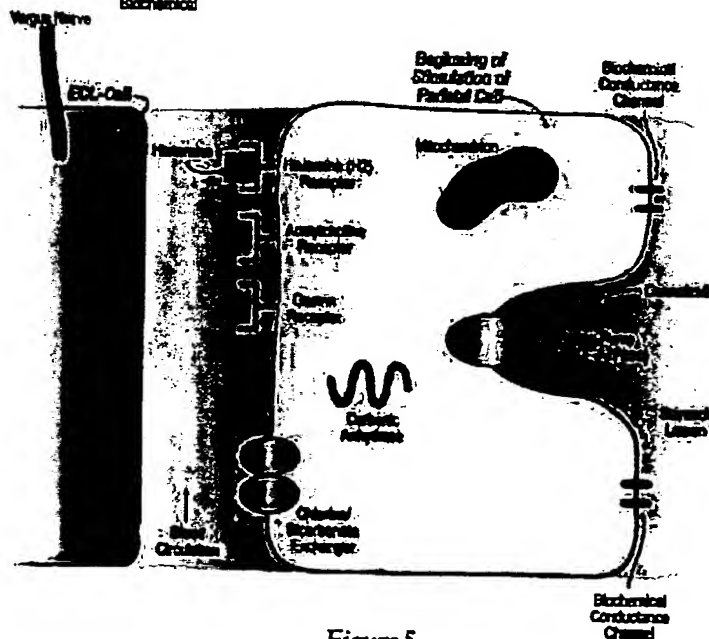


Figure 5

31. Although there are other receptors on the parietal cell with affinity for other organic molecules that were also believed potentially to participate in the stimulation of the parietal cell – notably acetylcholine (AC) (a neurotransmitter) and gastrin (secreted by other specialized cells in the stomach, called G-cells), the Histamine receptor plays an important role under usual conditions.

32. The biochemical reactions that make up the intervening events occur within the parietal cell after it is stimulated. They lead, *inter alia*, to the appearance of hydrogen ions ( $H^+$ ) (protons) in the cell as Figure 6 illustrates. Because the hydrogen ions ( $H^+$ ) appear in the stimulated cell, Dr. Soll in the Schleisinger and Fordtran textbook (see paragraph 23, *supra*.) calls this an acid “compartment” of the stimulated parietal cell. The stage is set for the next step, which is the activation of the “proton pump.”

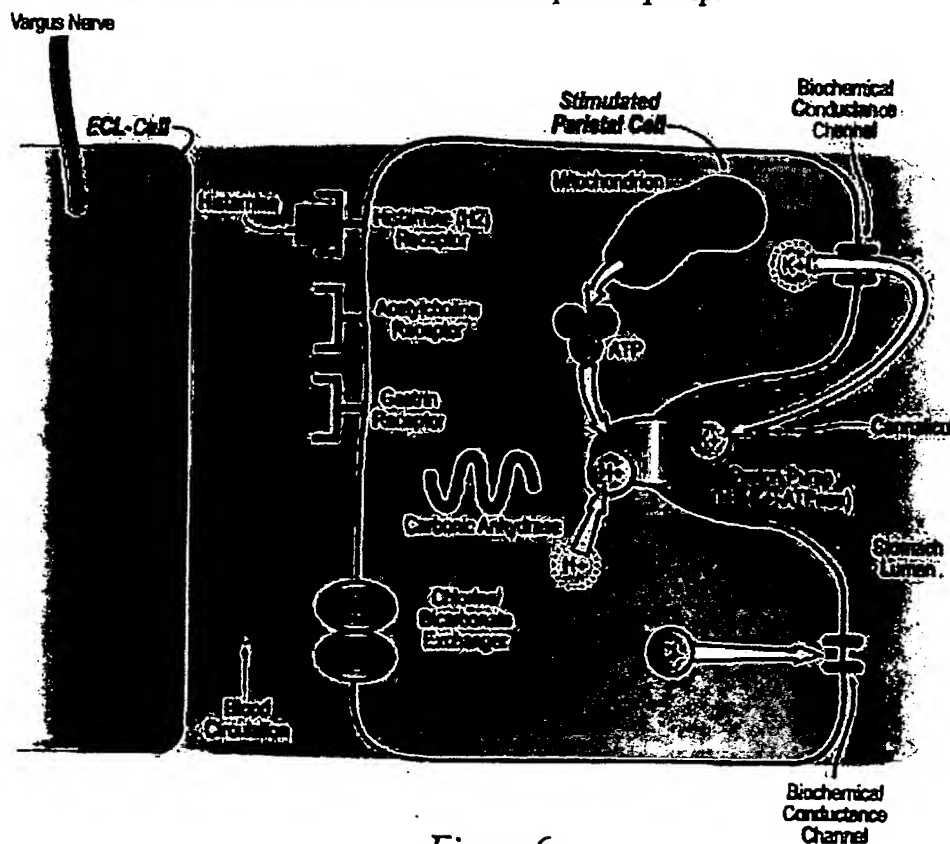


Figure 6



33. The end point of the biochemical reactions in the parietal cell is the activation of the proton pump to release a hydrogen ion ( $H^+$ ) into the stomach lumen. To release the hydrogen ion ( $H^+$ ), a special gastric enzyme exchanger is present in the parietal cell -- called hydrogen potassium -adenosine triphosphate (ATPase), or in shorthand, " $H^+$ ,  $K^+$ -ATPase," as Figure 6 illustrates. The hydrogen ion (proton)  $H^+$  inside the parietal cell and a potassium ion  $K^+$  in the stomach lumen bind to the  $H^+$ / $K^+$  -ATPase enzyme (Figure 6). Figures 6 and 7 also illustrate another chemical substance called adenosine triphosphate (ATP) that is generated by mitochondrion of the parietal cell. ATP is a source of chemical energy. The ATP binds to the  $H^+$ ,  $K^+$  -ATPase enzyme (Figure 7) to drive a conformational change in the  $H^+$ ,  $K^+$  -ATPase enzyme. This activates the proton pump. The proton pump transports a hydrogen ion ( $H^+$ ) out of the parietal cell into the canaliculi, in exchange for the potassium ion ( $K^+$ ) that enters the parietal cell. This in-and-out biochemical reaction is the ending point, and it is called the "proton pump." The proton pump is not a pump in a physical sense. It is a specialized biochemical reaction that occurs within a parietal cell. When bound by adenosine triphosphate (ATP), the  $H^+$ ,  $K^+$  -ATPase enzyme becomes the proton pump. Meanwhile, a chloride ion ( $Cl^-$ ) is transported into the stomach lumen through a biochemical conductance channel in the parietal cell wall to preserve electro-neutrality (see Figure 7). Gastric acid enters the main stomach lumen.

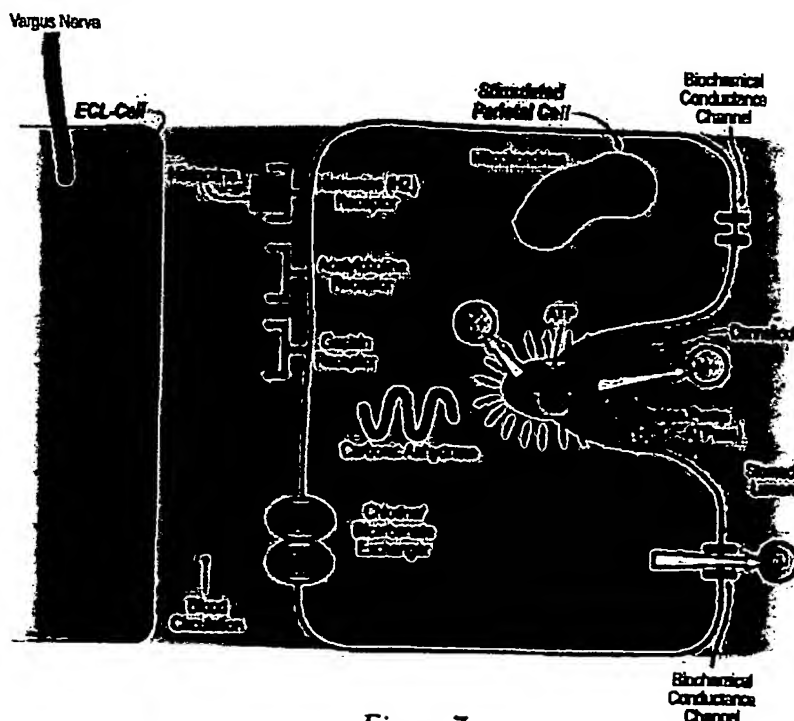


Figure 7

34. Between meals, a small number of parietal cells are producing gastric acid to keep the stomach environment acidic. This is called basal acid secretion. Stimulated acid secretion occurs when the parietal cells are stimulated by hormones or nerves. These biochemical pumps are created *de novo* by intracellular processes in response to stimulus. When the stimulus disappears, the proton pumps fade away.

35. From this perspective, the pharmacological effects of H2RA's and PPI's can be easily characterized, as we understood them at a time prior to the Invention. At a time prior to the Invention, my colleagues and I characterized the pharmacologic effect of H2RA's as one that blocks the H2 Receptors at the beginning point of the acid secretion process (this is illustrated in Figure 8).

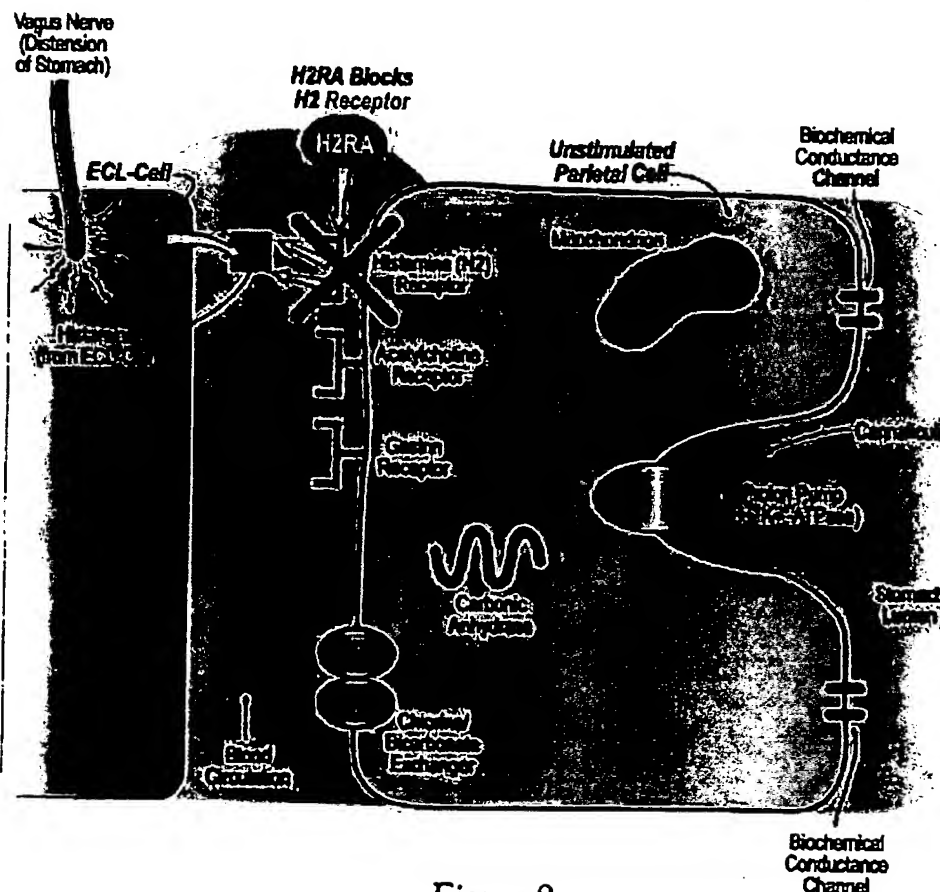


Figure 8

36. On the other hand, at a time prior to the Invention, my colleagues and I characterized the pharmacologic effect of PPI's as one that inactivates the proton pumps at the ending point of the acid secretion process (this is illustrated in Figure 9).

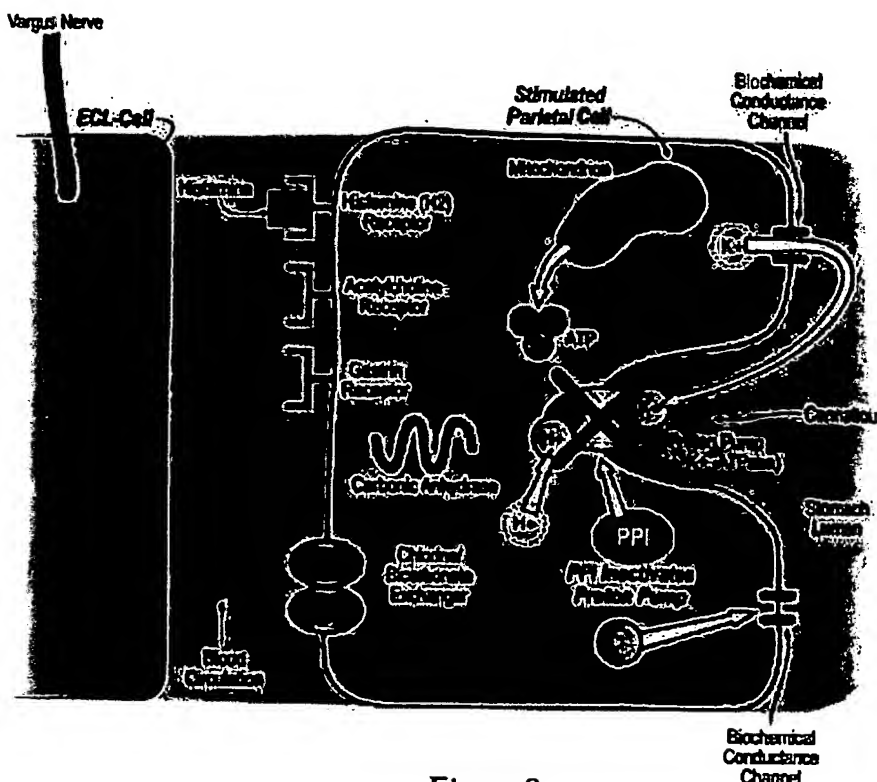


Figure 9

37. Further, and importantly, at a time prior to the Invention, my colleagues and I believed that PPI's would provide their pharmacological effect only if the parietal cell had been stimulated by histamine (as Figure 9 shows); that is, there needed to be a beginning point before the PPI could disable the ending point. This is what Dr. Soll means when he wrote in 1998 (see paragraph 23, *supra*.): "PPI's effectively inhibit only stimulated parietal cells." And this, in turn, is what led to Dr. Soll's teaching at the time: "Combination therapy [of PPIs] with H2RAs is never appropriate," (see paragraph 23, *supra*) as also stated by Drs. Wolfe and Sach (see paragraph 25, *supra*.): "Do *not* administer concomitantly with H2-receptor antagonists or postaglandins."

38. These teachings made sense at the time. The H2RA's work at the beginning point (Figure 8) -- they block the stimulation of the parietal cell in the first instance. By blocking the H2 Receptor, acid secretion by histamine stimulation is inhibited. H2RA's are therefore called antisecretory drugs because they inhibit acid secretion. .

39. The PPI's, on the other hand, work at the ending point (Figure 9), to inactivate the proton pump of a stimulated parietal cell. The PPI's bind irreversibly with the H<sup>+</sup>, K<sup>+</sup> -ATPase enzyme within the parietal cell to inactivate the H<sup>+</sup>, K<sup>+</sup> -ATPase enzyme -- and thereby inactivate the proton pump. The result is that no gastric acid is secreted. PPI's are thus another class of an "antisecretory" drug, again because they inhibit acid secretion.

40. An important aspect of the pharmacology of PPI's is that PPI's are physiologically inactive prodrugs, that are incapable of binding with the H<sup>+</sup>, K<sup>+</sup> -ATPase enzyme exchanger. To be capable of binding with the H<sup>+</sup>, K<sup>+</sup> -ATPase enzyme exchanger, the PPI's need to be activated, and this occurs *in situ* within the acid (H<sup>+</sup>) environment of the parietal cell (as Figure 9 illustrates). For activation to occur, and for the PPI to work, it had to be subjected to the acid environment of a stimulated, actively secreting parietal cell (as Figure 9 illustrates). This is precisely what the foregoing articles teach: "THE PARIETAL CELL HAS TO BE TURNED ON TO BE TURNED OFF BY OMEPRAZOLE [a PPI]." (see paragraph 23, *supra*).

41. At that time, my colleagues and I believed that, in the absence of a stimulated parietal cell, the PPI would remain inactive, unable to exert its effect and thereby served no purpose. Since H2RA's blocked the H2 Receptor, they blocked the stimulation of the parietal cell in the first instance, so the co-administration of a PPI with the H2RA simultaneously or concomitantly made no scientific or pharmacological sense to me or my colleagues at that time. However, for the same reason, it did make scientific and

pharmacological sense why it was never appropriate to co-administer a H2RA and PPI simultaneously or concomitantly.

42. At a time prior to the invention, my colleagues and I understood that the co-administration of H2RA and PPI would prevent the PPI from exerting its antisecretory effect, and that we would be doing the patient a disservice by not allowing the PPI to act. The concept was that one drug (the H2RA) bars the other (the PPI) from working, so if you gave the two together, they interfered with each other. Furthermore, PPI's were (and still are) expensive. Therefore, not only did we think that there was a potential therapeutic disadvantage when you combine these drugs, to co-administer would put the patient at an economic disadvantage. At a time prior to the invention, there was no scientific, clinical, or pharmacologic rationale for the co-administration of H2RA's and PPI's and, instead, all scientific and pharmacologic beliefs argued against it.

43. Dr. Wolfe is the inventor of United States Patent 5,229,137 (issued July 20, 1993) (Attachment 9) for his invention of the combination of antacid and H2RA's (Pepcid-AC®). Dr. Wolfe tried that combination, but did he did not try the Invention. On the contrary, Dr. Wolfe wrote articles advising against the concomitant administration of PPI's and H2RA's together (see paragraph 25, *supra*). This illustrates the thinking at the time: Dr. Wolfe's combination of an antacid and a H2RA was at the time scientifically logical: an antacid works in the stomach to neutralize gastric acid after it is secreted (this is illustrated in Figure 10), while an H2RA works in a parietal cell to block the H2 receptor to prevent secretion in the first place (which is illustrated in Figure 8). The pharmacologic mechanism of an antacid does not interfere with the pharmacological mechanism of a H2RA.

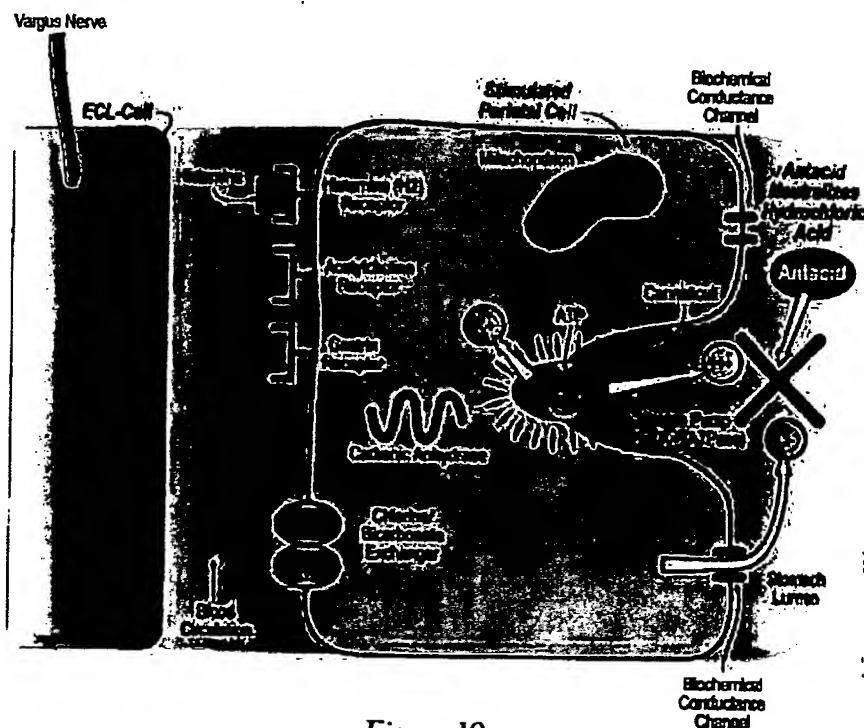


Figure 10

As the belief at the time was that the H2RA would inhibit the effect of the PPI, Dr. Wolfe advocated against co-administration of H2RA's and PPI's together. This, I believe, underscores my point: that the co-administration of a H2RA and PPI was at a time prior to the invention was considered scientifically illogical and no medical doctor would do it

when seeking to treat GERD. Dr. Wolfe is a prime example of the thought process at work in the field during the relevant time period prior to the Invention. Even in the treatment of nocturnal acid secretion of patients taking PPI's (see paragraph 18, *supra*), the administration of PPI's and H2RA's were separated in time to prevent interaction between the two drugs.

44. I co-authored a scientific paper based on the Invention with Drs. Fändriks, Lönroth, and Pettersson, which was published in the *Scandinavian Journal of Gastroenterology* (*Scandinavian Journal of Gastroenterology*, "Can Famotidine and Omeprazole be Combined on a Once-Daily Basis?" 2007; 42: 689-694) (Attachment 10). After data contained in the paper had been presented at a national meeting, I presented another paper at a state of the art lecture at a conference *Digestive Disease Week 2005 "New Advances in GI Pharmacotherapy: What New Agents will be Available in the Near Future?"* (May 14-19 2005, Chicago, Illinois) in which I discussed the potential of the administration of a PPI with a H2RA simultaneously or concomitantly. Immediately after my presentation, I recall that the very first question from the floor was along the lines of "why doesn't blocking the activation of the parietal cell with an H2RA make the PPI ineffective". It is not a surprise to me that this was the first question, as it was one that could be predicted to come from a colleague in the field at that time. I responded by concurring that the traditional view had always been that since an activated proton pump was required to make the PPI effective, co-administration with an H2RA would be counter-productive, but that the data showed that this was not the case, and we therefore needed to change our way of thinking. Following this, a lot of people came up to me and said this was interesting, because they had also shared the traditional view, but they had their eyes opened by looking at the data.

45. In the particular study described in the *Scandinavian Journal of Gastroenterology* (see paragraph 44, *supra*), we demonstrated that famotidine (H2RA) and omeprazole (PPI) could be co-administered and actually get an additive benefit in the early days of treatment. The data compared the control arms omeprazole alone;

famotidine alone; and co-administration of omeprazole and famotidine in the manner of the Invention (Attachment 10, see Table 1, on page 693). The data show for Day 1 (i) omeprazole alone controlled stomach acid pH >4 for 27% of the day, (ii) famotidine alone controlled stomach acid pH >4 for 54% of the day; and (iii) the co-administration of omeprazole and famotidine controlled the stomach acid pH >4 for 67% of the day. We therefore found a surprising effect on Day 1. The traditional view would have us believe that we would observe an adverse effect due to the co-administration, because we had co-administered a PPI with an H2RA. According to the prior knowledge, the control percentage for the co-administration (67%) should have been, if anything, lower than the individual control percentages, or certainly no greater than famotidine alone, yet it was higher than the individual control percentages for omeprazole alone (27%) and famotidine alone (54%). This was an unexpected novel finding. The other surprising aspect was that, on Day 8, when the steady state for the omeprazole had been reached, the percentage of time that omeprazole alone was controlling stomach acid was 78% of the day (which is in keeping with the pharmacological profile of a PPI); famotidine alone was controlling stomach acid for 48% of the day, which is similar to the 54% on Day 1, but showing hint of physiologic tolerance (also in keeping with the pharmacological profile of a H2RA, as I explained in Paragraph 18 *supra*); but the co-administration of PPI and H2RA was controlling stomach acid for 78% of the day, showing none of the expected diminished PPI activity compared to Day 1. According to the prior conventional wisdom, on Day 1 and Day 8 we would expect the control percentages for the co-administered dose to be lower than the individual doses. At the very least, we would expect the co-administered dose to be lower on Day 8 compared to the omeprazole alone, because we would expect that the effectiveness of omeprazole would be inhibited by the presence of H2RA. The data are totally the opposite as to what one would have expected.

46. Subsequent studies have demonstrated that the co-administration of other PPI's with famotidine in the manner of the Invention provide similar surprising results. Studies of the PPI esomeprazole co-administered with famotidine and of the PPI lansoprazole co-



administered with famotidine, each pair being administered simultaneously or concomitantly on a once daily basis for eight days, demonstrate that the co-administration of these PPI's with an H2RA simultaneously or concomitantly gives an early and clinically important intragastric pH increase within two hours after co-administration of the first dose, and that the acid-suppressive effect is maintained throughout the eight days treatment period.

47. The data are surprising and unexpected in that the co-administration of PPI and H2RA works at all, let alone better than the individual doses. We do not fully understand why this is the case at this time. This is why the Invention challenges my colleagues and me to look again at how these drugs work on acid secretion, and look at it from different perspectives than we have in the past. The Invention has changed our views, and the empirical data test or challenge a well held view. The data from our study show that acid inhibition by the Invention is prompt, additive, and prolonged, if desired.

48. The Invention provides me and my physician colleagues a therapeutic tool that did not exist before. Surprisingly, the Invention has shown that it is appropriate, to co-administer PPI and H2RA together simultaneously or concomitantly in the dosage form and dosage regime as I have described. The data show that co-administration of H2RA and PPI simultaneously or concomitantly in this manner leads to a prompt beneficial additive relief of symptoms on Day 1, and persists for a prolonged treatment period, if necessary, on demand.

49. I have been warned that willful false statements and the like are punishable by fine, or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon. All statements I have made of my own knowledge are true, and all statements made upon information and belief are believed to be true.



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Nimish Vakil, M.D., FACP, FACG

Dated this 21 day of April, 2009.

## Curriculum Vitae.

Updated: 1/09

**Nimish Vakil MD**  
**Clinical Professor of Medicine,**  
**University of Wisconsin School of Medicine and Public Health,**  
**Madison Wisconsin**

**Mailing address:**  
**W231 N1440 Corporate Drive, Suite 307,**  
**Waukesha WI 53186**  
**Telephone: 262-896-6400**  
**Fax: 262-896-8986**  
**E-mail: nvakil@wisc.edu**

### Faculty Appointments:

- University of Wisconsin Medical School, Madison, Clinical Professor of Medicine 7/1/97-present
- Marquette University College of Health Sciences, Clinical Associate Professor of Medicine, 2002-present
- University of Wisconsin                      Clinical Associate Professor                      7/1/93-6/30/97.
- University of Rochester                      Assistant Professor                      1988-1993.
- University of Texas                      Assistant Professor                      1987-88.

### Post-graduate Training:

- Northwestern University School of Medicine, Chicago, Illinois. Fellowship-Gastroenterology.  
July 1985-June 1987.
- New York Medical College Affiliated Hospitals, New York, New York-Internal Medicine Residency, July 1983-June 1985.
- University of Munich; Germany, Advanced Endoscopy under Professor M. Classen, Federal Republic of Germany, July 1987- October 1987.

### Medical School:

University of Bombay, Seth G.S. Medical College, Bombay, India

- MBBS 1980;
- MD (Internal Medicine) 1982.

**Certification:**

- American Boards of Gastroenterology, 1987
- American Boards of Internal Medicine, 1985
- Wisconsin license, # 34096

**Professional Organizations:**

- Fellow, American College of Gastroenterology.
- Fellow, American College of Physicians
- American Gastroenterological Association
- American Society for Gastrointestinal Endoscopy

**Editorial Responsibilities:**

2003 onwards: Associate Editor, American Journal of Gastroenterology

2006 Onwards: US Editor, Endoscopy

**Editorial Boards:**

2002-present. International Editorial Board, Alimentary Pharmacology and Therapeutics

2000- present. Editorial Board, Evidence based Gastroenterology

2000-present. Editorial Board, Digestive and Liver Disease

1999-2004. Editorial Board, American Journal of Gastroenterology

**Patient related Organizations:**

- Advisory Board, International Foundation for Functional Bowel Disorders, Milwaukee WI.
- Advisory Board, Cyclical Vomiting Association

**Honors and Awards:**

- 1998: Northwestern University Alumnus Award awarded May 1998 at the American Gastroenterological Association, New Orleans LA
- 1995: European H Pylori Study group, Edinburgh, Scotland. July 1995- First Prize for original research paper- Decision Analysis of the Economic Impct of Helicobacter Pylori eradication regimens.
- 1995: Certificate of appreciation from the American Society of Gastrointestinal Endoscopy for chairmanship of the ad hoc committee on networking.
- 1994: American Gastroenterological Association Junior Faculty Travel Award to the World Congress of Gastroenterology-1994.
- 1991: German Academic Exchange Research Study Award, Universities of Munich and Kassel, Germany.
- A Blaine Brower Traveling Fellowship of the American College of Physicians:  
- University of Munich, W Germany
- Chicago Gastroenterology Fellows Research Prize 1987.
- 1985: American College of Physicians Clinical Vignette Prize 1985.

## **Publications:**

### **Internal Medicine Journals:**

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#### **Invited papers/Editorials:**

1. VAKIL N. Functional Dyspepsia and PPIs : The devil in the details *Am J Med.* 2004 Jun 1;116(11):781-2



2. SHARMA P & VAKIL N. H pylori infection and GERD. *Aliment Pharmacol Ther.* 2003 Feb;17(3):297-305.
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### *National and International Professional Assignments:*

- Chair Quality of life Abstract review committee DDW 2008
- Dyspepsia, Quality of life review committees DDW 2007
- Chair Dyspepsia abstract review DDW 2006
- Chair Dyspepsia abstract review DDW 2006
- Chair Dyspepsia review section DDW 2004
- Associate Chair H pylori section DDW 2003
- 1998-2002: Chairman, Practice Parameters Committee, American College of Gastroenterology

- 2000-present: Publications and Guidelines Committee of the Organisation Mondiale de Gastroenterologie
- 2000-2001: Technology assessment committee of the American Society for Gastrointestinal Endoscopy
- DDW 2000: Associate Chair, H pylori section for DDW abstracts
- 1998-2000: Member, National Affairs Committee, American College of Gastroenterology
- 1998-2000: Member, Research Committee, American College of Gastroenterology
- 1993-4, 1994-5, 1995-1997, 1998-2000: Member, Medical Informatics Committee of the American Society of Gastrointestinal Endoscopy
- 1995-6, 1996-7, 1997-8: Member Practice Parameters Committee of the American College of Gastroenterology.
- 1993-4, 1994-5: Chairman, National Committee of the American Society of Gastrointestinal Endoscopy on "Networking in endoscopy".
- 1994-1995, 1995-1996: Health Information Technology sub-committee of the American Society for Parenteral and Enteral Nutrition.

# Nonerosive Reflux Disease— Current Concepts and Dilemmas

Ronnie Fass, M.D., M. Brian Fennerty, M.D., F.A.C.G., and Nimish Vakil, M.D., F.A.C.G.

*Section of Gastroenterology, Southern Arizona VA Health Care System and University of Arizona Health Sciences Center, Tucson, Arizona; Division of Gastroenterology, Department of Medicine, Oregon Health Sciences University, Portland, Oregon; and Section of Gastroenterology, Department of Medicine, University of Wisconsin Medical School, Milwaukee, Wisconsin*

## ABSTRACT

Nonerosive reflux disease is defined as the presence of typical symptoms of gastroesophageal reflux disease caused by intraesophageal acid in the absence of visible esophageal mucosal injury at endoscopy. Recent studies demonstrate that it is a chronic disease with a significant impact on quality of life, and it is very common in primary care settings. Treatment with acid inhibitory agents is effective, and proton pump inhibitors are the most effective form of therapy. (Am J Gastroenterol 2001;96:303–314. © 2001 by Am. Coll. of Gastroenterology)

## INTRODUCTION

Symptoms of gastroesophageal reflux disease (GERD) such as heartburn and acid regurgitation occur weekly in 20% of the adult population (1). The prevalence of reflux symptoms probably underestimates the true prevalence of GERD, as it is based solely on the presence of heartburn and/or acid regurgitation. Recent data indicate that many patients with GERD present with symptoms such as acid reflux–related chest pain (noncardiac chest pain), asthma, cough, and hoarseness, and lack concomitant symptoms of heartburn or acid regurgitation (2). For instance, it has been demonstrated that as many as 60–70% of adult asthmatics have GERD. Given the prevalence of asthma in the adult population in the United States as well as the millions of patients with noncardiac chest pain, cough, and hoarseness, the true prevalence of GERD is likely to be substantially greater than 20%.

Until recently our understanding of GERD was largely limited to patients with erosive esophagitis. Investigators and clinicians were concerned with erosive esophagitis for a number of reasons. Foremost among these was the need for an unequivocal criterion for the diagnosis of gastroesophageal reflux disease in clinical trials. This resulted in most of the literature on therapy being limited to patients with erosive esophagitis. The presence of erosive esophagitis also provided an objective means of measuring efficacy, as heal-

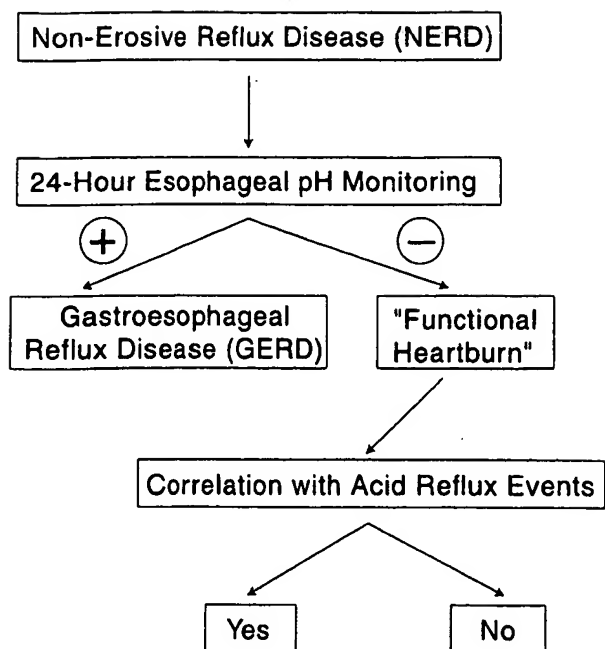
ing could be clearly defined. These trials fostered the development of numerous scoring systems of esophagitis (3, 4) furthering interest and limiting the focus of research in GERD to patients with erosive esophagitis. Compounding this research “bias” toward GERD patients with erosive esophagitis was the erroneous belief that the adverse clinical impact of GERD was limited to those with erosive esophagitis. This belief ignored accumulating data that the greatest clinical impact of GERD was on quality of life (QOL) and that the impairment was similar in patients with and without erosive disease (5). The assumption that therapeutic needs were not as great in patients with nonerosive reflux disease (NERD) has also been challenged by recent studies. NERD therefore represents an enormously important clinical problem that requires a refocus of our attention and a priority for clinical research.

In this article, we review what is known about the pathophysiology, diagnosis, and treatment of NERD, as well as its cost to society and to health care systems. We also identify critical areas where information is lacking, to shed further light on this enormously important clinical issue.

## DEFINITION

There is no generally agreed upon definition of NERD in the literature. We define NERD as the presence of typical symptoms of gastroesophageal reflux disease caused by intraesophageal acid, in the absence of visible esophageal mucosal injury at endoscopy.

It is clear that NERD is not composed of a homogeneous group of patients. The functional esophageal disorders committee that convened in Rome in 1990 suggested the use of 24-h esophageal pH monitoring as a tool to distinguish a subset of NERD patients as those with “functional heartburn” (6). Functional heartburn was defined as burning retrosternal discomfort for  $\geq 3$  months in the absence of pathological gastroesophageal reflux by 24-h esophageal pH monitoring and esophagitis by endoscopy. The committee suggested that further distinction between subgroups of functional heartburn patients could be achieved by correlating physiological acid reflux events with symptoms of heart-



**Figure 1.** Subcategorization of the nonerosive reflux disease (NERD) group by using 24-h esophageal pH monitoring and "symptom index," as suggested by the functional esophageal disorders committee in Rome in 1990 (6).

burn (Fig. 1). As the pH test is not a gold standard for the diagnosis of GERD, it may not be reliable in categorizing the NERD group (Figs. 2–4). False negative results are not uncommon and may occur even in patients with documented erosive esophagitis (7, 8). Furthermore, it has been demonstrated that 30–50% of NERD patients presenting with heartburn will have no evidence of pathological acid reflux by currently available diagnostic modalities (6, 9, 10).

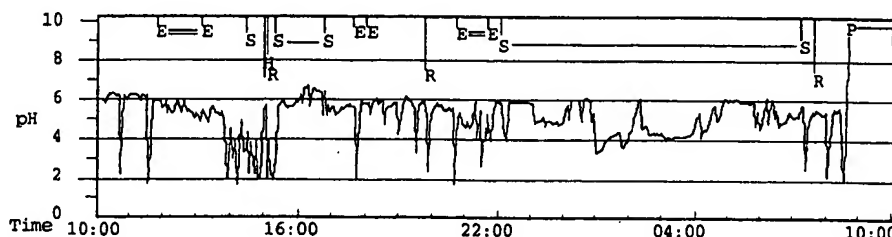
## EPIDEMIOLOGY AND NATURAL HISTORY

Gastroesophageal reflux disease represents a spectrum of symptoms and tissue damage. Patients may present with typical symptoms such as heartburn and acid regurgitation and/or atypical symptoms such as chest pain, hoarseness, and cough. In addition, patients may present with normal esophageal mucosa, mucosal inflammation, or complica-

tions such as stricture and Barrett's esophagus. It has been demonstrated that there is no correlation between the severity of GERD symptoms and the presence or absence of visible esophageal inflammation (11).

Early studies that originated from tertiary referral centers suggested that approximately half of the patients presenting with reflux symptoms had erosive esophagitis at upper endoscopy (11, 12). However, most patients with GERD either self-medicate and never seek medical attention, or they are seen and treated by community-based physicians (13). Recent studies that were carried out in community practice revealed that up to 70% of the GERD patients have NERD (14, 15). Therefore, erosive esophagitis does not seem to be as common as previously suggested. In another community-based study of antacid users, Robinson *et al.* found that 53% of GERD patients had NERD and two thirds of the remainder had only mild erosive changes at endoscopy (16). This study highlights another important finding that in community-based patients with esophageal mucosal injury, mild erosive esophagitis is the most prevalent form of mucosal injury.

Only a few studies, mostly retrospective, have assessed the natural history of NERD. In one study from Italy, 33 NERD patients were followed for a period of 6 months while on antacids and/or prokinetics (17). At the end of the follow-up period, 58% remained symptomatic and 15% had developed erosive esophagitis. A total of 42% became asymptomatic and were able to discontinue all medical therapy. There was no difference in the pattern of GERD between the symptomatic patients and those that became asymptomatic. However, this retrospective review offers only a short-term follow-up. In another study from Scotland, NERD patients with either excess or normal esophageal acid exposure but a positive symptom index were followed for a median period of 6.5 and 4.4 yr, respectively (18). In all, 87% of those with normal acid exposure and 79% of those with excess acid reflux remained symptomatic; 53% and 47%, respectively, recorded their symptoms as the same or worse than at the original presentation, despite regular use of medications in 60% of patients in each group. These studies and others suggest that most NERD patients will demonstrate a chronic pattern of symptoms with periods of exacerbation and remission. Further delineation of the clin-



**Figure 2.** A 24-h esophageal pH recording in a patient with nonerosive reflux disease (NERD). During the test the patient experienced three episodes of acid regurgitation (R) and one episode of heartburn (H). All symptoms correlate with acid reflux events, suggesting a 100% symptom index. (E = meal; S = supine position.)

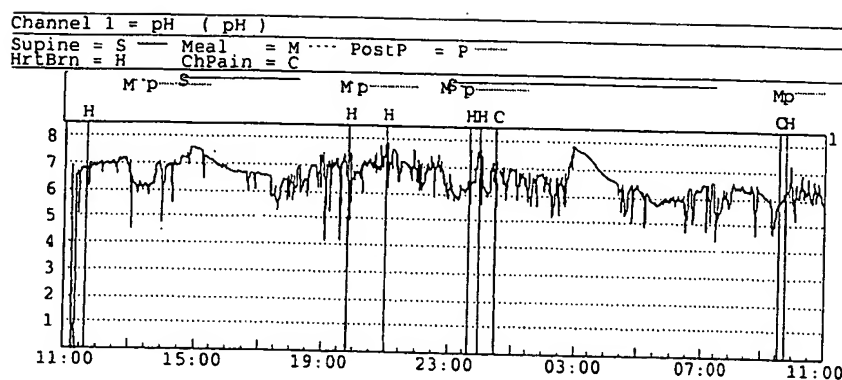


Figure 3. A 24-h esophageal pH recording in a patient with nonerosive reflux disease (NERD). Despite the lack of any acid reflux events, the patient reported six episodes of heartburn (H) and two of chest discomfort (C). Calculated symptom index is 0%.

ical characteristics of NERD patients over a longer period is needed.

### MECHANISMS OF HEARTBURN

Heartburn is the classic symptom of GERD that is perceived by patients with and without mucosal injury. In patients with erosive esophagitis, stimulation of sensory afferent pathways by acid refluxate or inflammatory mediators is considered to be the mechanism underlying symptom generation. The precise relationship between symptoms of heartburn and acid reflux events in patients with normal endoscopy remains to be established.

There is evidence for the presence of nerve terminals of both vagal and spinal fibers within the mucosa and muscle layer of the esophagus (19–22). However, the precise localization of specific intramural nerve structures that are responsible for the transmission of painfully perceived, afferent information is not yet known. It seems that activation of peripheral terminals of spinal rather than vagal afferents are a necessary condition (22). Polymodal vagal afferents with receptive fields in the esophageal mucosa are important in chemically or mechanically induced reflex regulation that is not associated with conscious perception under normal

conditions (19). Vagal afferents seem to have no role in visceral pain transmission, except for a pain-modulatory effect for certain types of vagal afferents and a role in perception of esophageal distension (23, 24). In contrast, spinal afferents are thought to be important for the transmission of discomfort and pain (25). The receptive fields for mechanosensitive spinal afferents are assumed to be located primarily in the muscle and serosa, whereas the intraepithelial nerve endings of spinal afferents are likely to be involved in the mediation of acid-induced pain during topical exposure to intraluminal acid (20).

The mechanisms that lead to symptoms of heartburn in patients lacking esophageal mucosal injury remain an area of intense research. In both animal models and humans, dilation of the intercellular spaces has been noted in acid-exposed tissues (26, 27). In humans, these findings were detected by transmission electron photomicrographs in patients with erosive and nonerosive reflux disease (27, 28). These findings may suggest that patients with reflux disease have an increase in paracellular permeability in the esophageal epithelium (29). Because sensory neurons in the esophageal epithelium reside within the intercellular spaces, the increase in paracellular permeability may explain heartburn symptoms during esophageal acid exposure in patients

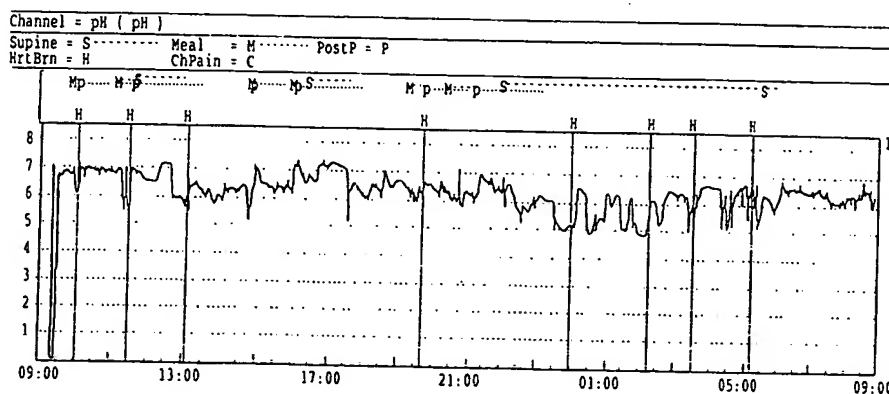


Figure 4. A 24-h esophageal pH monitoring in a patient with nonerosive reflux disease (NERD) who experienced eight episodes of heartburn (H). The heartburn episodes correlate very closely with minute changes in intraesophageal pH.

with NERD (29). However, this hypothesis provides only a partial explanation for the relationship between symptom generation and acid reflux events that has been observed in NERD patients.

It is currently accepted that an excess of intraesophageal acid and perhaps other components of duodenogastro-esophageal reflux are the primary causes for symptoms of heartburn in NERD patients. However, between 33% to 50% of the patients with NERD will have normal test results when they undergo initial 24-h esophageal pH monitoring, and up to 25% will reverse diagnosis (positive to negative test and *vice versa*) on subsequent pH testing (8, 14, 30–32). These data suggest that in a significant number of NERD patients, physiological acid exposure may be sufficient to cause typical symptoms of heartburn.

The specific role of the symptom index, which determines the percentage of symptoms that correlates with acid reflux events, remains to be elucidated in NERD (33). In addition, interpretation of a positive symptom index (>50%) in the setting of a normal pH test remains an area of controversy. Although some have considered it indicative of GERD (false negative pH test by conventional criteria), others have suggested that it might be indicative of a group of patients that is highly sensitive to physiological amounts of acid reflux (functional heartburn) (6, 9). Patients with abnormal upper endoscopy are more likely to experience heartburn symptoms (65%) during pH testing than patients with normal endoscopy and abnormal pH testing (32.5%) and those with both normal endoscopy and pH testing (21%) (34). In general, patients with erosive esophagitis are significantly more likely to have a positive symptom index when compared with NERD patients (33). Furthermore, patients with a normal upper endoscopy and 24-h pH test have a significantly lower calculated symptom index ( $26\% \pm 10.7\%$ ) than those with abnormal upper endoscopy ( $85\% \pm 4.6\%$ ) or normal endoscopy and abnormal pH testing ( $70\% \pm 7.1\%$ ). These data suggest that patients with a normal endoscopy and 24-h pH test are less likely to have an abnormal symptom index (34, 35). The symptom index data may mean that a subset of NERD patients with physiological acid reflux may have hypersensitivity to acid. It is also possible that other non-acid-related intraesophageal stimuli can trigger heartburn. Animal models of afferent nerve sensitization have demonstrated that acid exposure can sensitize esophageal nerve endings (chemoreceptors) directly or via inflammatory mediators, resulting in lower pain thresholds (36). The sensitized esophageal chemoreceptors are part of the spinal afferents, which mediate esophageal sensation. Altered pain perception demonstrated by increased chemoreceptor sensitivity to acid has been shown in NERD patients (37, 38). This hypersensitivity to acid can be demonstrated in both the proximal and distal esophagus (39). However, NERD patients seem to be less sensitive to acid when compared to patients with documented erosive esophagitis, regardless of their endoscopic grading (37, 40).

Assessment of mechanoreceptor sensitivity using intra-

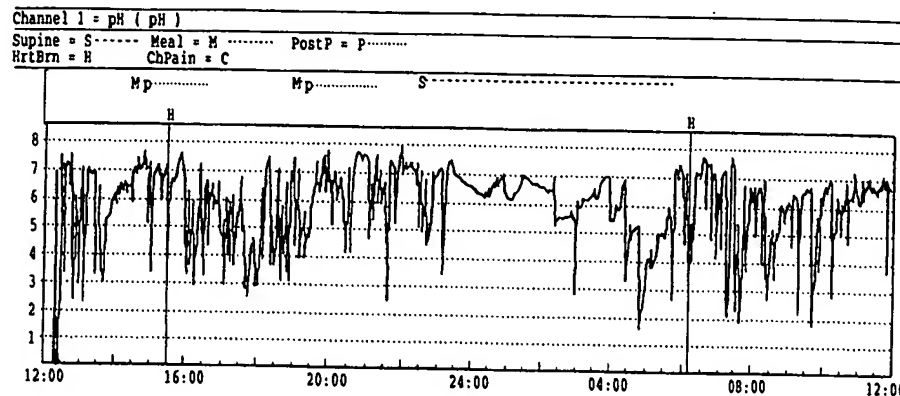
esophageal balloon distension has yielded contradictory results. Trimble *et al.* evaluated patients with heartburn and excess reflux defined by abnormal upper endoscopy and/or 24-h esophageal pH monitoring and compared them to patients with heartburn and a normal 24-h pH test; the results demonstrated that the latter group had lower volume thresholds for perception of esophageal balloon distension and discomfort (41). This study suggests that patients with typical heartburn who lack any evidence of excess acid are highly sensitive to mechanical stimuli. In another study using esophageal balloon distension delivered by an electronic barostat, patients with NERD and erosive esophagitis did not demonstrate an increase in mechanosensitivity, when compared to normal controls (37).

The current literature suggests that there is a differential effect of long-term esophageal acid exposure on chemosensitivity and mechanosensitivity in humans. Chronic esophageal exposure to excess acid affects chemosensitive but not mechanosensitive afferent pathways. Only patients with typical GERD symptoms and no evidence of excess acid demonstrate an increase in mechanosensitivity. Some experts hypothesize that the latter group might be sensitive to minute changes in pH that do not reach our current criterion for acid reflux event ( $\text{pH} < 4$ ) (Fig. 4). Data to support this intriguing hypothesis are still lacking. Thus far, the axiom has been that pathological amount of acid is the only visceral stimulus that can result in heartburn ("no acid, no heartburn"). However, as has been mentioned, heartburn may be reported when the extent of esophageal acid exposure is within the physiological range in patients with either a negative symptom index or a complete absence of any documented acid reflux events (38). These data suggest that non-acid-related stimuli may produce heartburn as well in a subset of patients with NERD.

In a recent study it has been demonstrated that chest pain and heartburn may be provoked in normal subjects during esophageal balloon distension either in the proximal or distal portion of the esophagus (37). Interestingly, volume thresholds for heartburn and chest pain in both esophageal locations were similar, suggesting that for a specific volume some patients will develop chest pain and others heartburn. Furthermore, volume thresholds for both chest pain and heartburn did not differ significantly at each esophageal location and between locations. In this study, esophageal balloon distension also reproduced typical heartburn symptoms in patients with documented GERD who were being treated with high-dose proton pump inhibitors. This study clearly demonstrates that acid is not the only visceral stimulus that may lead to heartburn. Pehlivanov *et al.* suggested that longitudinal muscle contractions of the esophagus, detected only by high frequency intraluminal ultrasound and not by traditional esophageal manometry, are the motor equivalent of heartburn sensation (42). These contractions may occur in the presence or absence of acid reflux. This intriguing observation requires further confirmation.

The data discussed so far suggest that NERD patients





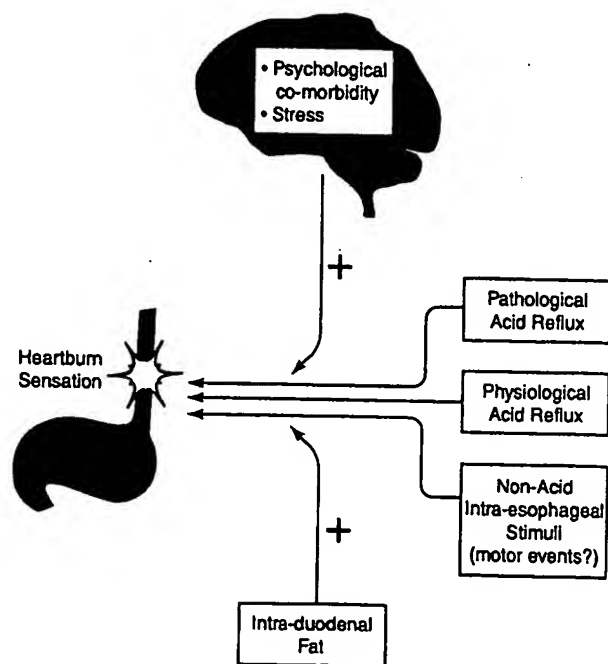
**Figure 5.** A 24-h esophageal pH recording in a patient with nonerosive reflux disease (NERD). The patient experienced multiple acid reflux events but perceived and developed heartburn during only two of them. This pH recording clearly demonstrated that most acid reflux events are not sensed.

might have either excessive or physiological acid exposure or even non-acid-related intraesophageal stimuli that result in the sensation of heartburn. However, it is well known that only the minority of acid reflux events (<20%) are associated with symptoms of heartburn (Fig. 5) (43). It is still unclear what factors determine whether an acid reflux event will reach a conscious level. It seems that most acid reflux events that are perceived occur postprandially (Fig. 5). Recently it has been demonstrated that intraduodenal fat infusion enhances perception of intraesophageal acid and may be a major modulator of postprandial GERD symptoms (44). Stress and psychological comorbidity seem also to be important factors in the generation of symptoms in patients with GERD. In a Gallup poll, 64% of individuals with heartburn reported that stress increased their symptoms (45). Through brain-gut interaction, stress may induce alterations in GI secretory and motor responses, however, it remains to be demonstrated how stress exacerbates GERD symptoms and whether it has a specific role in NERD patients.

Intraesophageal pH measurements in both normal subjects and GERD patients fail to demonstrate an increase in acid reflux events during psychologically induced stress (46–48). Furthermore, acute stress does not induce significant changes in esophageal motility in patients with NERD (49). However, interventions aimed at reducing stress in patients with GERD (hypnosis and progressive muscle relaxation technique) have resulted in subjective improvement in reflux symptom ratings (48, 50). Bradley *et al.* suggested that chronically anxious patients when exposed to prolonged stress might perceive low intensity esophageal stimuli as a painful reflux symptom (41). They and others have postulated that anxious patients may devote an excessive amount of attention to a wide variety of esophageal events (*i.e.*, they are hypervigilant) and thus may perceive such events as painful (47, 49).

Baker *et al.* (51) performed psychological assessment in patients with documented GERD and controls. Patients with reflux differed from controls on scales of depression, somatization, anxiety, and intensity of reporting symptom dis-

tress. In a secondary analysis it was shown that only 30% of the GERD patients accounted for the differences between the groups, suggesting that although most patients with GERD are psychologically similar to patients without GERD, a subset of psychologically distressed patients are more likely to be found among patients with GERD. Johnston *et al.* (52) studied patients with episodes of heartburn that did not correlate with acid reflux events (*i.e.*, patients with a negative symptom index). These patients were found to have significantly higher levels of trait anxiety and significantly less adequate social support structures



**Figure 6.** A proposed mechanistic model for heartburn sensation in patients with nonerosive reflux disease (NERD). Central and peripheral factors may enhance the perception of intraesophageal stimuli and are probably major modulators of symptoms in NERD patients.

when compared with patients with heartburn who had a positive symptom index. Stress and psychological comorbidity seem to have an important role in symptom generation in patients with GERD and, in particular, those with NERD. This emerging concept suggests that by modulating brain-gut interactions, symptom perception and possibly pathological events in the esophagus of GERD patients might be altered.

Figure 6 is a conceptual model that summarizes the mechanisms that are responsible for the sensation of heartburn in patients with NERD. It is likely that patients with NERD are a heterogeneous group with different mechanisms responsible for their symptoms. Some patients experience heartburn caused by excess acid reflux; others demonstrate esophageal chemoreceptor sensitivity to physiological amounts of acid. Another subgroup of patients will develop heartburn symptoms as a result of non-acid-related intraesophageal stimuli (possibly motor events). The latter subgroup, despite the presence of typical heartburn, does not meet the criteria for our definition of NERD. Central factors such as stress and peripheral factors such as intraduodenal fat may enhance the perception of various intraesophageal stimuli and thereby modulate symptoms in patients with NERD.

### PHYSIOLOGICAL CHARACTERISTICS

Assessment of esophageal motor function in patients with NERD reveals minor motility abnormalities compared to normal subjects. Patients with NERD have a slightly higher rate of primary peristalsis failure, defined by nontransmitted contractions or peristaltic contractions that do not traverse the entire esophageal body (53). Similarly, the mean amplitude of contractions in the distal esophagus and the mean lower esophageal sphincter pressure are mildly reduced (53). NERD patients rarely demonstrate lower esophageal sphincter pressures <10 mm Hg in contrast to patients with documented erosive esophagitis.

Assessment of esophageal acid exposure is limited by the lack of a gold standard for diagnosing gastroesophageal reflux disease. By using ambulatory 24-h esophageal pH monitoring it seems that NERD patients in general have slightly higher mean acid exposure than normal subjects and significantly less acid exposure than patients with erosive esophagitis (54, 55). This relationship is also maintained when esophageal acid exposure is evaluated either in the erect or supine positions (56).

By using the Bilitec 2000 (Medtronic, Minneapolis, MN), which detects bilirubin pigment spectrophotometrically, duodenogastroesophageal (DGER) reflux has been assessed in patients with GERD (57). The combination of both acid reflux and DGER correlated well with severity across the GERD spectrum. Esophageal exposure to both acid and DGER occurred in 50% of NERD patients as compared to 79% of patients with erosive esophagitis, 89% with uncomplicated Barrett's esophagus, and 100% of those with com-

plicated Barrett's esophagus. Further research concerning the role of DGER in NERD patients is needed.

### INVESTIGATION

In patients presenting with heartburn, unless alarm symptoms (such as dysphagia, bleeding, or weight loss) are present, empirical therapy is currently considered the standard of care (58). Using high-dose proton pump inhibitors (PPIs) for a short time, the PPI therapeutic trial as an initial diagnostic approach is a potentially simple, accurate, and cost-effective diagnosis strategy in patients with GERD (8, 30, 31, 59). It was found that over a period of 7 days, the symptom response rate of patients with NERD markedly improved from 27.2% to 83.3% when the omeprazole dose was increased from 40 mg once daily to 40 mg *b.i.d.* (59). This important study provides evidence that NERD patients also require a potent antireflux therapy for symptom control. Currently, there are no other studies using PPI therapeutic trials as a diagnostic tool in patients with NERD.

Upper endoscopy should be performed in all patients who present with alarm symptoms. The use of endoscopy as a screening tool for Barrett's esophagus remains controversial. Although recently, practice guidelines regarding Barrett's esophagus screening have been proposed by the American College of Gastroenterology, there is currently no consensus regarding at what point patients with GERD should be evaluated (60).

In patients undergoing upper endoscopy without esophageal mucosal injury, the addition of mucosal biopsy to detect histological changes consistent with GERD remains a common practice. The presence of inflammatory cells (neutrophils and eosinophils), epithelial hyperplasia (basal cell hyperplasia and elongated papillae), and dilated vessels in the papillae have all been considered to be markers of esophageal injury secondary to GERD in patients with intact-appearing mucosa (61). Using endoscopy and GERD symptoms as comparators, only 47.8% of NERD patients and 21.6% of normal controls had GERD-related histological findings in biopsies obtained 4 cm above the esophagogastric junction (62). In another study, histological findings typical of GERD were detected in 46% of NERD patients with abnormal pH testing, in 9% of those with normal pH tests, and in 29% of healthy controls (63). It seems from these studies that esophageal mucosal biopsies in NERD patients have a low yield and may not help to establish a diagnosis.

Diagnostic evaluation in NERD becomes increasingly important in patients who fail to respond to a standard dose of PPI. Failure of symptom control in NERD patients receiving PPI once a day (standard dose) is currently considered an indication for 24-h esophageal pH monitoring (64). However, when 57 NERD patients who continued to have symptoms of heartburn on a standard dose PPI underwent pH testing, the results were within the normal range in 61.1% (65). The extent of symptom control during therapy

with standard dose PPI seems to be related to the extent of intraesophageal acid exposure in the distal esophagus (51). The greater the total time that pH is initially  $<4$ , the better the symptom control. Thus, NERD patients with a mildly abnormal or normal pH test will often fail standard dose PPI treatment. This may be explained by either hypersensitivity to acid reflux in the physiological range, which may suggest the need for high dose PPI for complete acid elimination and consequent symptom control or by nonacid intraesophageal stimuli. A recent study demonstrated no increase in esophageal chemosensitivity to acid in NERD patients who failed standard dose PPI (31).

### QUALITY OF LIFE

A number of studies have demonstrated an impairment of quality of life in chronic erosive esophagitis. Tew *et al.* (66) studied the illness behavior of patients with NERD and found that these patients were similar to those with erosive esophagitis. Treatment improved both groups equally. In general, patients with GERD experience more pain and greater impairment in social functioning and emotional well-being than patients with other chronic diseases such as diabetes and hypertension. For example, Chal *et al.* found impairments in comfort (vs pain), vitality, and mental health in GERD (67). Dimenas reported impaired psychological well-being scores in patients with GERD (5). A small number of studies have evaluated patients with uninvestigated heartburn in primary care (68). Rust *et al.* demonstrated that impairment in quality of life was related to GERD symptoms and improved with therapy (ranitidine 150 mg *b.i.d.*) (69). Revicki *et al.* (70) studied 533 patients with a history of heartburn for 6 months before and after therapy with ranitidine, 150 mg *b.i.d.* Patients reported significantly worse scores on all eight scales of the SF-36 (physical function and well-being, emotional well-being) compared to the general population. Successful treatment led to marked improvement in the quality of life (70). Carlsson *et al.* (71) studied patients with endoscopy-negative reflux disease. The Psychological General Well-Being index (PGWB index) was used as a subjective measure of quality of life. Quality of life was impaired in patients with endoscopy negative disease and patients with erosive esophagitis and there were no significant differences between the groups. Omeprazole therapy improved the quality of life in both groups of patients (71). A recent study showed substantial improvement in quality of life with adequate therapy. Havellund *et al.* (72) studied quality of life using well validated scales in 163 patients with NERD. Quality of life was restored with omeprazole 10 mg or 20 mg and was comparable to that in the general population. Impairment of quality of life appears to be similar in patients with NERD and patients with erosive esophagitis. There is a strong association between symptoms and impairment of quality of life. Adequate treatment of symptoms therefore improves quality of life in patients with NERD.

### TREATMENT OF NERD

There are numerous therapeutic options available for treating patients presenting with symptoms of GERD or otherwise suspected as having this disease. Generally these therapeutic options have been viewed in a hierarchy of therapeutic efficacy, ranging from lifestyle modifications/antacids to histamine-2 receptor antagonists (H2RAs)/prokinetics to proton pump inhibitors (PPIs), with surgery reserved for those with continued symptoms or complications of GERD (73). It has been generally assumed by clinicians that patients with NERD would rarely demonstrate an incomplete response to either lifestyle modifications or therapy with H2RAs/prokinetics; thus, potent anti-secretory therapy with PPIs or surgery should rarely be necessary in this patient population. However, there is now ample evidence that this assumption is incorrect, and that the therapeutic requirements of patients with NERD are similar to those with erosive esophagitis.

Some of the first evidence that H2RAs may be less than optimal as therapy for NERD came from a large US study of patients with heartburn treated with famotidine (74). In this trial,  $<30\%$  of patients treated with H2RA twice daily had complete elimination of heartburn at 30 days, and little more than 50% of patients had relief at the end of 3 months. A sizable number of patients in this trial had NERD or minimal grades of esophagitis. Thus, indirectly, evidence began to suggest that patients with NERD might not be as easily treated as previously assumed. This should not have been surprising, given the pharmacology of H2RAs. These agents have been known to be ineffective in inhibiting meal-stimulated acid secretion and are associated with the rapid development of pharmacological tolerance (73). These pharmacological properties affect all patients with GERD, regardless of the presence of erosive esophagitis. Further support for the inadequacy of these agents in many patients with NERD is derived from a recent trial in which symptomatic GERD patients with an incomplete response to therapy with 3 months of a twice daily dose of an H2RA, were randomized to a further 2 months of continued therapy at this dose or to 2 months of a double dose of the H2RA (75). Further therapeutic response to continued use of an H2RA, even at high doses, was very modest in this trial.

Given the pharmacological deficiencies of H2RAs in controlling acid secretion it was felt that perhaps patients with NERD could be better served by using a prokinetic agent. Prokinetics had shown some efficacy in patients with erosive esophagitis, and it was hoped even greater efficacy could be demonstrated in patients with NERD. However, in a large European study, remission of symptoms could be maintained in fewer than half of those patients with NERD who were receiving cisapride (76). Thus, like what had been observed for H2RAs, the therapeutic efficacy of prokinetics in patients with NERD is limited. Concerns about the safety of cisapride also limit its utility in this setting.

There are data that indicate overwhelmingly that, in pa-

tients with erosive esophagitis, PPIs provide superior healing and symptom relief compared to H2RAs or prokinetics (77). Similar data are emerging regarding the use of PPIs in patients with NERD. In a 4-wk study of patients with heartburn and normal endoscopy, omeprazole resulted in complete symptom relief in nearly 60% of patients *versus* approximately 20% of those receiving placebo (78). In a similar placebo-controlled trial, symptom relief at 4 wk was also approximately 60% in those receiving omeprazole *versus* 24% of those in the placebo arm (51). There were further interesting observations made in this study. The therapeutic response was correlated with intraesophageal acid exposure: those patients with the greatest intraesophageal acid exposure had the greatest response (response rate, >85% in patients with an esophageal pH of <4 more than 10% of the time, *vs* 54% in patients with a pH of <4 less than 4% of the time). Thus, in NERD patients with an abnormal pH study, the therapeutic response was nearly identical to that seen in patients with erosive esophagitis. The study also indicated that in those patients with functional heartburn, a therapeutic response would be much less likely.

There are now trials comparing the therapeutic efficacy of PPIs *versus* H2RAs and cisapride in patients with NERD. In one study, 60% of patients treated with omeprazole had relief of heartburn, *versus* 40% of those receiving H2RAs (79). In that study, >50% of patients were maintained in remission with omeprazole, *versus* <30% of those patients receiving ranitidine. Similarly, in a study in the US, lansoprazole has also been shown to be more effective than ranitidine in relieving symptoms of reflux in patients without esophagitis (80). Similar therapeutic superiority for PPIs has been shown in another trial comparing omeprazole to cisapride (81). In that study, 63% of omeprazole patients were free of heartburn at 4 wk, *versus* 46% of those receiving cisapride. These results that demonstrate superiority of omeprazole over placebo in patients with NERD have also been confirmed in recent US studies (82).

Although further studies are needed to clarify the efficacy of agents in NERD, certain conclusions can be made based on the evidence available in the literature. First, the therapeutic efficacy of antisecretory agents seems overall to be lower in patients with NERD compared to those with erosive esophagitis. Whether this is related to the inclusion of patients without GERD in these studies (thus diluting a treatment effect) or whether it is attributable to some other factor is unclear. Second, the hierarchy of efficacy of therapy (PPI efficacy is greater than that of H2RA/prokinetics, which is greater than lifestyle modifications alone) that is seen in patients with erosive esophagitis is comparable for patients with NERD. Third, patients with NERD demonstrate a similar lack of efficacy to H2RAs, as do those with erosive esophagitis. The results of surgery in patients with NERD have been thought by many clinicians to be poorer than the results obtained in patients with esophagitis. However there are few data to support this clinical impression. It is likely that patients selected for surgery based on complete

symptom response to antisecretory therapy will have symptom outcomes similar to those seen with esophagitis. NERD patients who do not respond to antisecretory therapy are unlikely to have an optimal response to antireflux surgery. Controlled trials of antireflux surgery are needed to determine the role of this therapy in patients with NERD.

## ECONOMICS OF ENDOSCOPY NEGATIVE REFLUX DISEASE

The costs of managing chronic disease are of increasing importance in an era of constrained resources. Determining the optimal therapy for patients with NERD is a growing area of interest and research.

### *Costs of Reflux Disease in the United States*

Acid-related disorders are common problems in the US, and GERD is the most prevalent of these disorders. Given the frequency of the condition, there are surprisingly few data on the total cost of managing reflux disease. In large measure, this is because information systems used in most institutions are not able to capture disease-specific costs throughout the entire episode of care. Levin *et al.* (83) reported the cost of managing reflux disease in a managed care organization in California (Kaiser Permanente of Northern California) and calculated the GERD-related costs in a cohort of 1500 patients with acid-related disorders. The total annual HMO expenditures for acid-related disorders was \$59 million for a membership of 2.4 million members. The total annual direct cost of managing a GERD patient was \$4574 with a total pharmacy cost of \$491, outpatient costs of \$2403 (pharmacy, outpatient visits, etc.), and inpatient costs of \$1680. With adjustment of the data to determine the costs attributable to GERD separately, the total cost of managing GERD was \$471 per person, with pharmacy costs accounting for \$156 of this amount and outpatient costs accounting for \$279; in comparison, inpatient costs were small at \$35/per person. In the first 6 months after the diagnosis, outpatient costs remain the highest component cost of GERD management, accounting for a large proportion of the adjusted costs (\$246 out of a total of \$289).

### *Outpatient Costs*

Outpatient costs of managing GERD are related to office visits and endoscopic or radiological procedures. GERD is one of the most frequent indications for upper endoscopy in the United States. In a large database of >17,000 endoscopic procedures, GERD was the third leading indication for endoscopy (84). With the understanding of the frequency of endoscopy-negative reflux disease, it has become appreciated that endoscopy may fail to establish a diagnosis of reflux disease, and alternative strategies have been proposed. Chief among these is a trial of therapy in primary care settings. Several studies have compared a short trial of acid inhibitory therapy as a diagnostic test for reflux disease to investigations such as a 24-h esophageal pH monitoring or endoscopy. They found that a trial of therapy may be an

effective method to diagnose patients with suspected reflux disease who present with symptoms of heartburn or chest pain. Ofman *et al.* reported the cost-effectiveness of the omeprazole test in patients with noncardiac chest pain (85). In patients with a cardiac cause excluded by comprehensive cardiac evaluation, the omeprazole test with no subsequent investigations for patients who respond, and with sequential testing with ambulatory 24-h esophageal pH monitoring, esophageal manometry, and endoscopy reserved for patients who do not respond, was the most effective and least expensive strategy. Using a selective strategy of investigation in nonresponders to a trial of a proton pump inhibitor, the authors calculated that a 43% reduction in procedures would result and that the cost-savings would be \$454 per patient compared with a strategy of beginning with endoscopy followed by pH testing and esophageal manometry. Similarly, in patients with suspected reflux disease, the omeprazole test was estimated to reduce the number of endoscopies performed by 64% and the number of pH studies by 53%, with \$348 saved per patient evaluated (86). Similarly in asthmatic patients, cost-effectiveness analysis suggests that a trial of therapy with omeprazole 20 mg/day for 3 months, with 24-h esophageal pH monitoring reserved for nonresponders, was cost-effective (87).

Sonnenberg *et al.* performed a decision analysis comparing empirical therapy *versus* diagnostic testing in GERD (88). Empirical therapy was cost saving, with investigation reserved for nonresponders, despite the cost associated with an occasional incorrect diagnosis. However, as the duration of therapy becomes longer (>10 yr in this particular model), investigation becomes more meaningful because maintenance therapy in patients who do not need therapy increases costs. Again, because of the relatively high cost of surgery, a specific diagnosis is favored in this subgroup of patients.

#### *Is Endoscopy Useful in Managing Therapy?*

Recent studies have examined the role of endoscopy in the management of patients with GERD. In a prospective study of 664 patients with symptoms of GERD who were undergoing upper endoscopy in clinical practice, 74% of patients who had Barrett's esophagus or erythema, erosions or ulceration at endoscopy had an increase in therapy after endoscopy (89). In contrast, 35% of patients who had a normal endoscopy had an increase in therapy. These data suggest that endoscopy may influence the treatment prescribed by physicians. However the increase in treatment in most cases was based on persistent symptoms or on findings in the stomach or duodenum. Blustein *et al.* evaluated the utility of endoscopy in a large group of 742 patients. In all, 68% of patients who were still symptomatic on H2Ras were switched to omeprazole regardless of the findings at endoscopy, whereas 47% of patients taking omeprazole were maintained on the same therapy regardless of the findings at endoscopy (90). Endoscopy therefore had a limited role in determining therapy.

#### *Relief of Anxiety With Endoscopy*

In dyspepsia, it has been suggested that endoscopy may relieve anxiety and reduce subsequent health care use (91). These data are based on uncontrolled studies of small groups of patients. Other studies have shown a short-term improvement in quality of life after endoscopy in dyspeptic patients (92). A recent study in a large cohort of patients suggested that patients with a high degree of anxiety before endoscopy continued to have high degrees of anxiety after a normal endoscopy and reassurance from the endoscopists. Patients with low levels of anxiety did not obtain significant benefit (93). A subgroup of patients with moderate anxiety did demonstrate lasting improvement of anxiety after a normal endoscopy. Endoscopy may therefore be useful in very selected patients for the relief of anxiety, and may be helpful in anxious patients with atypical symptoms of GERD, *e.g.*, chest pain.

#### *Pharmacy Costs*

A number of economic models have examined the cost-effectiveness of treatment strategies for the management of erosive esophagitis, but there are few economic analyses on management strategies in endoscopy-negative reflux disease. Economic models that are directed at erosive esophagitis have limited applicability to unselected patients in primary care. Sonnenberg *et al.* examined a stepwise approach to the management of GERD in the VA system. They evaluated a stepwise strategy beginning with a generic H2RA; patients who failed to respond were treated with a higher dose of H2RA therapy, and those who still failed to respond were treated with proton pump inhibitors (step-up therapy) (94). This economic model suggested that an average of \$916 per patient could be saved every 5 yr by using a step-up strategy. In contrast, preliminary data from a clinical trial in primary care suggest that neither step-up or step-down therapy provided optimal control of heartburn over a 20-wk period (95). Recently a multicenter, randomized, open-label trial was performed in patients with symptoms of GERD in primary care practices in West Virginia. A total of 268 patients were randomized to received omeprazole 20 mg once a day or ranitidine (brand-name) 150 mg *b.i.d.* for up to 6 months. At 6 months, there was no significant difference in total costs between the groups, but symptoms were better controlled in the omeprazole group (96). These data suggest that effective therapies, which are more expensive to acquire, may still be cost-effective over relatively short periods of time because their higher efficacy decreases outpatient costs related to treatment failure.

As the natural history of endoscopy negative reflux disease is benign, control of symptoms is the principal determinant of the success of therapy. To reduce the cost of chronic maintenance therapy, alternate forms of maintenance therapy are being attempted in nonerosive reflux disease. New techniques of maintenance therapy offer significant advantages. These techniques consist of dose reduction or intermittent use of medication to reduce costs while

still achieving the goal of symptom relief. In a recent study, 677 patients with endoscopy-negative or mild-to-moderate erosive GERD in primary care were randomized to ranitidine 150 mg *b.i.d.*, low-dose omeprazole (10 mg/day), or standard dose omeprazole (20 mg/day) for 2 wk (97). If they had symptom relief they continued with the maintenance phase of the study, in which they received 2-wk courses of intermittent therapy with the regimen that had worked in the first instance. At the end of 1 yr of maintenance therapy, half of the patients did not require treatment for at least 6 months of the study period and had good control of symptoms, thus substantially reducing the cost of maintenance therapy. A cost analysis based on this study found no difference between the cost of the omeprazole and ranitidine arms, using cost assumptions from a number of European countries that were part of the trial. These data suggest that on a cost basis, there is little to be gained from a step-up approach to treating NERD (98).

Another alternative is to give on-demand therapy, thereby reducing the amount of medication being used. In one study, 424 patients with endoscopy negative reflux disease were randomized to placebo or PPI (omeprazole 20 mg or omeprazole 10 mg) on demand (99). At 6 months follow-up, 29% of patients had failed to respond to on-demand therapy and needed daily maintenance therapy. However 83% of patients randomized to on-demand therapy with omeprazole 20 mg a day were satisfactorily maintained over the 6-month time frame. The mean number of omeprazole capsules used per day was 0.43, suggesting that the total medication use was reduced by approximately 50%. In the future, patients with NERD will increasingly be managed with alternative forms of maintenance therapy. Some conclusions regarding the economics of NERD can be made from the available data. First, the cost of managing all forms of reflux disease is high. Second, outpatient costs are the major component of the management costs of NERD. Third, endoscopy—although useful for diagnosis—has little role in management, which is driven by symptoms. Fourth, new methods of PPI administration may be an interesting new option in the management of NERD, combining highly effective therapy with less frequent administration, thereby reducing cost.

In conclusion, NERD is a common condition in primary care. Many patients with NERD have moderate-to-severe symptoms and significant impairment in the quality of life. Therapy with acid-suppressive agents results in complete resolution of symptoms in the majority of patients and restores quality of life. Current data from surgical studies are inadequate to determine whether surgical therapy results in better or worse outcomes than medical therapy. Alternative methods of treatment including on-demand therapy and intermittent therapy deserve further study and may help to reduce the costs of maintenance therapy.

Reprint requests and correspondence: Nimish Vakil, M.D., University of Wisconsin Medical School, Sinai Samaritan Medical

Center, 945 North 12th Street, Room 4040, Milwaukee, WI 53233-1305.

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## RULES AND REGULATIONS

contained in the monograph. Products which do not meet both of these requirements shall be subject to the requirements for Category I products. If testing promptly undertaken but data adequate to prove effectiveness are not submitted to the Food and Drug Administration within the 2-year period, the ingredients listed in this category will no longer be permitted, even in a product that meets the in vitro antacid effectiveness standard, because of a lack of evidence that these ingredients make a meaningful contribution to the claimed effect for the product.

1. *Alginic acid*. Although the ingestion of alginic acid-containing products may produce a layer of material floating on top of the gastric contents, the available evidence is insufficient to demonstrate clinical effectiveness. The studies are fragmentary, uncontrolled, and few in number. No evidence is presented as to reproducibility of results. There is insufficient evidence that alginic acid-containing antacid products, even if they do produce a floating layer on top of the gastric contents, are clinically beneficial. Indeed, such evidence as there is indicates that these products do not increase the pH of gastric contents as a whole. Since regurgitation of gastric contents is particularly apt to occur when patients are lying down rather than in the upright position, alginic acid-containing products may be less beneficial than a standard antacid which is more likely to increase the pH throughout the gastric contents.

Alginic acid is safe in amounts usually orally (e.g., 4 grams per day) in antacid products.

*Attapulgitte (activated)*. This ingredient is safe in the amounts usually taken orally in antacid products.

3. *Charcoal, activated*. Charcoal is presently considered safe in amounts usually taken orally in antacid products, but study is specifically needed to determine whether the charcoal used contains benzpyrene or methylcholanthrene type carcinogens. Since charcoal-containing products may decrease absorption of certain oral drugs, the label shall bear the following drug interaction precaution: "Drug Interaction Precautions: Do not take this product if you are presently taking any prescription drug."

4. *Gastric mucin*. This ingredient is safe in the amounts usually taken orally in antacid products.

5. *Kaolin*. Kaolin is safe in amounts usually taken orally in antacid products. Since kaolin affects gastrointestinal absorption, kaolin interferes with the absorption of lincomycin, and therefore the label shall bear the following drug interaction precaution: "Drug Interaction Precautions: Do not take this product if you are presently taking a prescription antibiotic drug containing lincomycin."

6. *Methylcellulose*. Methylcellulose is safe in amounts usually taken orally (e.g., 2 grams per day in antacid products).

7. *Pectin*. Pectin is safe in the amounts usually taken orally in antacid products.

8. *Carboxy methylcellulose*. Carboxy methylcellulose is safe in amounts usually taken (e.g., 3 grams per day) in antacid products.

B. *Labeling*. Marketing under the following labeling conditions may continue for a period of 2 years after the date of publication of this determination subject to the same requirements specified above for the use of Category III ingredients.

1. OTC products containing ingredients listed in Category I or III are often used to treat symptoms that are not known to be related to acidity of gastric contents. These products may or may not qualify as antacids by the in vitro acid neutralizing test. The symptoms include "indigestion", "gas", "upper abdominal pressure", "full feeling", "nausea", "excessive eructations", "upset stomach", and the like. Some of these symptoms are vague, most are poorly understood as to pathophysiological mechanism, and none has been shown by adequate and reliable scientific evidence to be caused by or alleviated by changes in gastric acidity.

2. Claims or indications which link certain signs and symptoms, such as "sour breath", "upper abdominal pressure", "full feeling", "nausea", "stomach distress", "indigestion", "upset stomach", and "excessive eructations" with normal or hypernormal gastric acidity, are unproven since the relationship of such signs and symptoms to gastric acidity is unknown or dubious and there is no adequate and reliable scientific evidence to support these claims. Such claims or indications encourage the user to draw conclusions as to the cause or intermediation of such symptoms, a conclusion that even the medical profession is incapable of drawing at this time.

3. The evidence currently available is inadequate to support the claim that such properties as "floating", "coating", "defoaming", "demulcent", and "carminative" contribute to the relief of upper gastrointestinal symptoms. The continued use of such claims, or ones closely allied to them, requires additional studies both to confirm the claimed specific action and to demonstrate clinical significance.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-42 as amended, 1050-53 as amended, 1055-56 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to the Commissioner (21 CFR 2.120) and based upon the administrative record in this proceeding, Title 21 of the Code of Federal Regulations is amended by adding Parts 331 and 332 (formerly §§ 130.305 and 180.306) to Subchapter D to read as follows:

|        |  |
|--------|--|
|        | Subpart A—General Provisions                                 |
| Sec.   |  |
| 331.1  | Scope.   |
|        | Subpart B—Active Ingredients                                 |
| 331.10 | Antacid active ingredients.                                  |
| 331.11 | Listing of specific active ingredients.                      |
| 331.16 | Combination with nonantacid active ingredients.              |
|        | Subpart C—Testing Procedures                                 |
| 331.20 | Apparatus and reagents.                                      |
| 331.21 | Determination of percent contribution of active ingredients. |
| 331.22 | Reagent standardization.                                     |
| 331.23 | Temperature standardization.                                 |
| 331.24 | Tablet disintegration test.                                  |
| 331.25 | Preliminary antacid test.                                    |
| 331.26 | Acid neutralizing capacity test.                             |
| 331.29 | Test modifications.  |
|        | Subpart D—Labeling   |
| 331.30 | Labeling of antacid products.                                |
| 331.31 | Professional labeling.                                       |

## Subpart A—General Provisions

## § 331.1 Scope.

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

## Subpart B—Active Ingredients

## § 331.10 Antacid active ingredients.

(a) The active antacid ingredients of the product consist of one or more of the ingredients permitted in § 331.11 within any maximum daily dosage limit established, each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product, and the finished product contains at least 5 mEq. of acid neutralizing capacity and results in a pH of 3.5 or greater at the end of the initial 10-minute period as measured by the method established in § 331.25. The method established in § 331.21 shall be used to determine the percent contribution of each antacid active ingredient.

(b) This section does not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

## § 331.11 Listing of specific active ingredients.

(a) Aluminum-containing active ingredients:

(1) Aluminum carbonate.  
(2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisulfate codried gel, aluminum-hydroxide-sucrose powder hydrated).

(3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminoacetic acid.

(4) Aluminum phosphate, maximum daily dosage limit 8 grams.

(5) Dihydroxyaluminum sodium carbonate.

(b) Bicarbonate-containing active ingredients: Bicarbonate ion; maximum

daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.

(c) Bismuth-containing active ingredients:

- (1) Bismuth aluminate.
- (2) Bismuth carbonate.
- (3) Bismuth subcarbonate.
- (4) Bismuth subgallate.
- (5) Bismuth subnitrate.

(d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).

(e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.

(f) Glycine (aminoacetic acid).

(g) Magnesium-containing active ingredients:

(1) Hydrate magnesium aluminate activated-sulfate.

- (2) Magaldrate.
- (3) Magnesium aluminosilicates.
- (4) Magnesium carbonate.
- (5) Magnesium glycinate.
- (6) Magnesium hydroxide.
- (7) Magnesium oxide.
- (8) Magnesium trisilicate.
- (h) Milk solids, dried.

(i) Phosphate-containing active ingredients:

(1) Aluminum phosphate; maximum daily dosage limit 8 grams.

(2) Mono or dibasic calcium salt; maximum daily dosage limit 2 grams.

(3) Tricalcium phosphate; maximum daily dosage limit 24 grams.

(j) Potassium-containing active ingredients:

(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.

(2) Sodium potassium tartrate.

(k) Sodium-containing active ingredients:

(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older, and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder.

(2) Sodium potassium tartrate.

(3) Silicates:

- (1) Magnesium aluminosilicates.
- (2) Magnesium trisilicate.

(m) Tartrate-containing active ingredients. Tartaric acid or its salts; maximum daily dosage limit 200 mEq. (16 grams) of tartrate.

§ 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to cor-

rect for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antifatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

#### Subpart C—Testing Procedures

##### § 331.20 Apparatus and reagents.

- (a) pH meter, equipped with glass and saturated calomel electrodes.
- (b) Magnetic stirrer.
- (c) Magnetic stirring bars (about 40 mm. long and 10 mm. in diameter).
- (d) 50 ml. buret.
- (e) Buret stand.
- (f) 100 ml. beakers.
- (g) 250 ml. beakers.
- (h) 10 ml., 20 ml. and 30 ml. pipets calibrated to deliver.

$$\text{Percent contribution} = \frac{\text{Total mEq. Antacid Active Ingredient} \times 100}{\text{Total mEq. Antacid Product}}$$

##### § 331.22 Reagent standardization.

Standardize the sodium hydroxide (NaOH) and Hydrochloric acid (HCl) solutions according to the procedures in the United States Pharmacopeia XVIII (NaOH page 1036 and HCl page 1034) or the Official Methods of Analysis of the Association of Official Analytical Chemists, 11th Ed., 1970, (NaOH page 876 and HCl page 873).

##### § 331.23 Temperature standardization.

All tests shall be conducted at  $25^{\circ} \text{C} \pm 3^{\circ}$ .

##### § 331.24 Tablet disintegration test.

A tablet disintegration test shall be performed on tablets that are not to be chewed following the procedures described in the United States Pharmacopeia XVIII (page 932). If the label states the tablet may be swallowed, it must disintegrate within a 10-minute time limit pursuant to the test procedure using simulated gastric fluid test solution without enzymes, the United States Pharmacopeia XVIII page 1026, rather than water as the immersion fluid.

##### § 331.25 Preliminary antacid test.

(a) pH meter. Standardize the pH meter at pH 4.0 with the standardizing buffer and check for proper operation at pH 1 with 0.1 N HCl.

(b) Dosage form testing—(1) Liquid sample. Place an accurately weighed

(i) Tablet comminuting device.

(j) A number 20 and 100 U.S. standard mesh sieve.

(k) Tablet disintegration apparatus.

(l) 0.1 N, 0.5 N and 1.0 N hydrochloric acid.

(m) 0.5 N sodium hydroxide.

(n) Standard pH 4.0 buffer solution (0.05 M potassium hydrogen phthalate).

(o) 95 percent ethanol.

(p) Distilled Water.

##### § 331.21 Determination of percent contribution of active ingredients.

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250 ml. beaker. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix thoroughly to wet the sample (ethanol may affect the acid neutralizing capacity). Add water to a volume of 70 ml. and mix on magnetic stirrer at  $300 \pm 30$  r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.26 and calculate the percent contribution of the antacid active ingredient in the total product as follows:

(calculate density) and well mixed amount of the antacid product equivalent to the minimum labeled dosage; e.g., 5 ml., into a 100 ml. beaker. Add sufficient water to obtain a total volume of about 40 ml. and mix on magnetic stirrer at  $300 \pm 30$  r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.25.

(2) Chewable and non-chewable tablet sample. Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 100 ml. beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve.) Mix the sieved material to obtain a uniform sample. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may effect the acid neutralizing capacity). Add water to a volume of 40 ml. and mix on magnetic stirrer at  $300 \pm 30$  r.p.m. for about one minute. (Capsules should be tested in the same manner using the sieved capsule powder as the sample.) Analyze the sample according to the procedure set forth in § 331.25.

(3) Effervescent sample. Place an amount equivalent to the minimum labeled dosage into a 100 ml. beaker. Add 10 ml. water and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml. of water and swirl the beaker gently. Wash down the walls of the beaker with 20 ml. of water and

<sup>1</sup> Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, DC 20044.

## Review article: cost-effectiveness of different GERD management strategies

N. VAKIL

University of Wisconsin Medical School, Milwaukee, WI, USA

### SUMMARY

Recent data on gastro-oesophageal reflux disease management strategies suggest that the indirect costs of reflux disease are high, and that inadequate treatment is

associated with significant out-patient costs for patients. Long-term management strategies now focus on discontinuous therapy for some subgroups of patients. On-demand therapy is particularly attractive for patients who have no mucosal disease.

### INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a chronic condition in many cases and frequently requires prolonged therapy. Although complications are infrequent, the symptoms of reflux disease have a profound effect on quality of life and work performance, making GERD an expensive disease to manage. Health-related expenditures are generally described as direct costs (the costs of providing and obtaining treatment) and the indirect costs (other costs due to the disease such as time lost from work that are not related to the provision of health care). When different management strategies are compared, the cost of each strategy must be balanced against its effectiveness. The best innovation increases therapeutic efficacy but costs less than standard therapy. While this is a laudable goal, most innovations increase both cost and effectiveness and the trade-off between the increased cost and effectiveness must be determined by cost-effectiveness studies. There are three general approaches to the management of any chronic disease: (i) Reduce costs regardless of outcome, (ii) Improve outcomes regardless of cost, and (iii) Maximize outcomes within the constraints of available resources. Cost-effectiveness studies help to optimize

clinical outcomes within the constraints of available resources.

### THE COST OF REFLUX DISEASE IN THE USA

The costs of managing GERD have been measured in managed care settings in the USA. It is remarkable, despite the frequency of the disease, that the cost of treating GERD has not been studied more rigorously. Most of the studies done to date have focused entirely on direct medical costs but emerging data suggest that the indirect costs of GERD may be significant and deserve more attention.

Levin *et al.*<sup>1</sup> reported the cost of managing reflux disease in a managed care setting (Kaiser Permanente of Northern California). They calculated the GERD-related costs in a cohort of patients with acid related disorders. The total annual expenditures for acid-related disorders were \$59 million. With adjustment of the data to determine the costs attributable to GERD, the total cost of managing GERD was \$471 per person, with pharmacy costs accounting for \$156 of this amount and out-patient costs accounting for \$279, while in-patient costs were small at \$35/per person. In the first 6 months after diagnosis, out-patient costs remain the highest component cost of GERD management, accounting for a large proportion of the adjusted costs (\$246 out of a total of \$289). These data suggest that pharmacy costs account for a small proportion of the

Correspondence to: Dr N. Vakil, University of Wisconsin Medical School, Sinai Samaritan Medical Center, 945 North 12th Street, Room 4040, Milwaukee, WI 53233, USA.  
E-mail: nvakil@facstaff.wisc.edu

total costs of acute or chronic management of the disease. Another cost of illness study showed that drugs accounted for approximately 50% of the total direct costs of GERD treatment.<sup>2</sup> GERD has also been shown to cause significant losses through time off work and reduced productivity while at work, and also to reduce productivity during regular daily activities.<sup>3</sup> The indirect costs of the disease need to be considered in economic assessments of GERD.

#### PHARMACEUTICAL COSTS AND TREATMENT STRATEGIES

Proton pump inhibitor therapy is more effective than H<sub>2</sub> receptor antagonist therapy in erosive GERD. A number of economic models have compared the costs of H<sub>2</sub> receptor antagonist therapy to proton pump inhibitor therapy in erosive oesophagitis in the acute and long-term management of erosive GERD. Not surprisingly, given the high efficacy of proton pump inhibitor therapy, these studies have suggested that a proton pump inhibitor-based strategy is cost-effective when cost-effectiveness determinations are based on comparisons with H<sub>2</sub> receptor antagonists.<sup>4, 5</sup> More recent studies have compared the costs of proton pump inhibitors to generic H<sub>2</sub> receptor antagonists, which are now widely available. Goeree *et al.*<sup>6</sup> used the cost of generic ranitidine in Canada in their base case analysis. The cost of generic ranitidine in Canada is \$Can 0.44 per tablet vs. \$Can 2.42 per tablet for omeprazole. In this model, maintenance therapy with proton pump inhibitor had better clinical outcomes, but was not the dominant strategy. In an economic model based on clinical trials comparing esomeprazole and omeprazole for the treatment of acute erosive GERD, the cost-effectiveness of esomeprazole 40 mg and omeprazole 20 mg over an 8-week period was compared.<sup>7</sup> The esomeprazole strategy was found to be dominant over the omeprazole strategy. Time with GERD (defined as the time with endoscopic evidence of erosions) was 2.9 weeks in the esomeprazole group and 3.6 weeks in the omeprazole group. Zagari *et al.*<sup>8</sup> used a decision analytic model, and estimated the 1-year direct cost of treating patients with proton pump inhibitors (\$1192) to be lower than the total cost for a branded H<sub>2</sub>-RA (\$1495), and comparable to a generic H<sub>2</sub>-RA (\$1152).

While most models have focused on groups of patients with erosive oesophagitis, Sonnenberg *et al.* examined a systematic approach to the management of GERD in the

Veterans Administration system in the USA. They evaluated a strategy beginning with a generic H<sub>2</sub>-RA. Failures with this strategy would be treated with a higher dose of H<sub>2</sub>-RA therapy, and failures to the latter treated with proton pump inhibitors (step-up therapy).<sup>9</sup> This economic model suggested that an average of \$916 could be saved per patient every 5 years by using a step-up strategy. Clinical data from the same group in this population suggests that this strategy may be effective in clinical practice.<sup>10</sup> In contrast, data from a clinical trial in primary care suggest that neither step-up or step-down therapy provided optimal control of heartburn over a 20-week period.<sup>11</sup> Results from a recent multicentre, randomized open-labelled study with economic end-points provides some interesting results. Patients with symptoms of GERD (uninvestigated) in primary care practices in West Virginia were evaluated. A total of 268 patients were randomized to omeprazole 20 mg once a day or ranitidine 150 mg (brand-name) b.d. for up to 6 months. At 6 months, there was no significant difference in total costs between the groups, but the symptoms were better controlled in the omeprazole group.<sup>12</sup> This study showed that, while the initial acquisition costs of proton-pump inhibitor therapy may be higher, the overall costs may be similar because of the poorer efficacy in the H<sub>2</sub>-RA group.

A recent study evaluated the cost of management strategies employed by managed care organizations.<sup>13</sup> This was a prospective randomized economic trial in four large managed care organizations. A total of 685 patients with GERD were randomized to omeprazole 20 mg or ranitidine 150 mg b.d. for 4 weeks. Additional 4-week therapy was given to patients as required. Investigations and office visits were determined over the 16-week period by usual practice. Omeprazole was more effective in controlling symptoms in these patients. Patients spent more money for over-the-counter heartburn remedies in the ranitidine group than did patients treated with omeprazole. As most pharmacy data systems do not capture information on over-the-counter medications, many economic evaluations fail to account for the costs associated with inadequate therapy.

#### DISCONTINUOUS MAINTENANCE THERAPY: PATIENT-DRIVEN AND COST-EFFECTIVE?

The understanding that many patients with reflux disease have no mucosal injury has led to the exploration of other forms of treatment that control symptoms

and decrease costs by reducing the frequency with which medication is administered. These techniques consist of dose reduction or the discontinuous use of medication to reduce costs while still achieving the goal of complete symptom relief. In a recent study, 677 patients with endoscopy negative or mild-moderate erosive GERD in primary care were randomized to ranitidine 150 mg b.d., low-dose omeprazole (10 mg) or standard dose omeprazole (20 mg) for 2 weeks.<sup>14</sup> If they had symptom relief, they continued with the maintenance phase of the study where they received 2-week courses of intermittent therapy with the regimen that had worked in the first instance. At the end of 1 year of maintenance therapy, approximately half the patients did not require treatment for at least 6 months of the study period, despite satisfactory control of symptoms. A cost analysis based on this study found no difference between the costs of the omeprazole or ranitidine arms, using cost assumptions from a number of European countries that were part of the trial. These data suggest that on a cost basis, there is little to be gained from a step-up approach in patients with endoscopy-negative reflux disease.<sup>15</sup> This study demonstrated that the use of short intermittent courses of therapy in patients with mild erosive reflux disease or nonerosive reflux disease is cost-effective.

Studies in primary care have shown that many patients with GERD do not take medications on a regular basis and frequently take them on an as-needed basis.<sup>16</sup> As a result, the concept of 'on-demand' therapy has gained importance. On-demand therapy is particularly interesting in patients with nonerosive reflux disease because they have no discernable mucosal disease and the main purpose of treatment is to alleviate the patient's symptoms. In one study, 424 patients with endoscopy-negative reflux disease were randomized to placebo or proton pump inhibitor (omeprazole 20 mg or omeprazole 10 mg) on demand.<sup>17</sup> At 6 months follow-up, 29% of the patients had failed on demand therapy and needed daily maintenance therapy. However 83% of patients randomized to on-demand therapy with omeprazole 20 mg a day were satisfactorily maintained over the 6-month time frame. The mean number of omeprazole capsules used per day was 0.43, suggesting that the total medication use was reduced by approximately 50%. In a recent study of esomeprazole therapy, 320 patients with endoscopy-negative reflux disease who had complete symptom resolution after 4 weeks of therapy

with either esomeprazole 20 mg or omeprazole 20 mg, were randomized to receive esomeprazole 20 mg on-demand or placebo on-demand for 6 months.<sup>18</sup> Medication intake was measured using electronic chips embedded in the caps of the medication containers. On average, esomeprazole was taken once every 3 days and 86% of patients were managed with on-demand therapy compared to 49% in the placebo group. These data suggest that on-demand therapy is effective and can substantially reduce costs.

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## Novel methods of using proton-pump inhibitors

Nimish Vakil, MD

*University of Wisconsin Medical School, Aurora Sinai Medical Center,  
945 North 12th Street, Room 4040, Milwaukee, WI 53233, USA*

Proton-pump inhibitors (PPIs) are used widely in the treatment of gastro-esophageal reflux disease. On-demand therapy with PPIs has been shown to be effective in patients with nonerosive reflux disease or mild erosive reflux disease. This strategy can reduce the cost of maintenance therapy and is appealing in patients with no evidence of mucosal disease. The long-term efficacy and safety of on-demand PPI therapy have not been established. Nocturnal reflux may be important in patients with complicated reflux disease or Barrett's esophagus. Data on combining PPIs with H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) suggest that nocturnal gastric pH can be controlled by the administration of H<sub>2</sub>RAs at bedtime. There are few data on nocturnal symptoms, and some studies suggest that tachyphylaxis may develop with H<sub>2</sub>RA therapy. More data are required on the clinical effectiveness of combination therapy administered long-term.

Proton-pump inhibitors (PPIs) are used widely in the treatment of gastro-esophageal reflux disease (GERD). Although the disease is chronic in most patients, relapses occur infrequently in some patients. Many patients with GERD do not take maintenance medications daily. A significant disadvantage with all currently available PPIs is their relatively high cost. New approaches to managing patients with PPIs are designed to reduce the cost of maintenance therapy by decreasing the frequency of administration. These strategies of on-demand and intermittent PPI therapy are discussed in this article. Studies have suggested that many patients who currently are taking PPIs have a nocturnal drop in gastric pH that may last 1 hour or longer.

*E-mail address:* nvakil@facstaff.wisc.edu

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### On-demand or intermittent therapy

GERD is a chronic disease, and many patients who have healing and symptomatic relief with a short course of therapy eventually relapse. Studies have suggested that many patients with GERD do not take PPIs on a daily basis even when they are prescribed as such. Clinical studies have been done in patients with continuous and discontinuous therapy, and these studies have suggested that a proportion of patients may be managed effectively by discontinuous therapy. Discontinuous therapy may be intermittent or on-demand. Intermittent therapy is the administration of short predetermined courses of therapy when symptoms recur. The course may be 1 or 2 weeks in duration. On-demand therapy is patient driven, and there are no fixed durations of therapy. Instead, patients are told to take medications when they are symptomatic for as long as they think it is necessary. Discontinuous therapies are of interest because they reduce medication cost and may decrease the rebound in acid secretion seen after prolonged continuous therapy.

In a study of intermittent therapy, 677 patients with endoscopy-negative reflux disease or Los Angeles grade A or B erosive esophagitis in a primary care setting were randomized to ranitidine, 150 mg twice a day; low-dose omeprazole, 10 mg daily; or standard-dose omeprazole, 20 mg daily, for 2 weeks [1]. If the patients had symptom relief, they continued with the maintenance phase of the study, in which they received 2-week courses of intermittent therapy with the regimen that had worked in the first instance. Of the 677 patients entering the study, 318 reached the 1-year time point with intermittent therapy, without a need for daily maintenance therapy. Omeprazole, 20 mg, was significantly superior to ranitidine at week 2. The long-term response was similar, however, in the responders in the three groups. Of patients, 22% to 27% required daily maintenance and 46% to 48% were managed with intermittent therapy for the ensuing 12 months. Most patients relapsed infrequently on intermittent treatment; 271 (40%) had no relapses, and 203 (30%) had one, 102 (15%) had two, and 54 (8%) had three relapses. The median number of days without treatment for the entire cohort was 142 days. Approximately half the population did not need therapy for at least 6 months of the year of maintenance therapy. A cost analysis based on this study found no difference between the cost of the omeprazole arm and the ranitidine arm, suggesting using cost assumptions from many European countries that were part of the trial. These data suggest that on a cost basis, there is little to be gained from stepping down to intermittent  $H_2$ -receptor antagonist ( $H_2RA$ ) therapy after initial treatment with a PPI [2].

In a short-term study of on-demand therapy with low-dose  $H_2RA$  therapy, Galmiche et al [3] showed that ranitidine administered in a dose of 75 mg three times a day on demand was effective in the short-term relief of heartburn (defined as a 75% improvement of symptoms). Of patients, 41% reported improvement in heartburn in this short-term trial of 15 days.

Two studies evaluated the efficacy of on-demand PPI therapy over longer periods. In one study, 424 patients with endoscopy-negative reflux disease were randomized to placebo or PPI (omeprazole, 20 mg, or omeprazole, 10 mg) on demand [4]. Over the 6-month follow-up period, 29% of patients failed on-demand therapy and required daily maintenance therapy. Of patients randomized to on-demand therapy with omeprazole, 20 mg/d, 83% were maintained satisfactorily over the 6-month time frame. The mean number of omeprazole capsules used per day was 0.43, and the total amount of medication used was reduced by approximately 50%. In a study of esomeprazole therapy, 320 patients with endoscopy-negative reflux disease who had complete symptom resolution after 4 weeks of therapy with either esomeprazole, 20 mg, or omeprazole, 20 mg, were randomized to receive esomeprazole, 20 mg, or placebo on-demand for 6 months [5]. Patients were permitted to use antacids as rescue medications. Patients were instructed to take no more than one dose of the medication a day for the relief of heartburn and to stop when the symptoms were controlled adequately. Medication intake was measured using electronic data recorders mounted into the caps of the medication containers. A total of 110 patients discontinued therapy because of insufficient control of heartburn (14% in the esomeprazole group and 51% in the placebo group). In the esomeprazole group, 52% of patients took medications for a maximum of 3 days at a time, as measured by the electronic sensors in the cap of the medication bottle. In the esomeprazole group, 22% of patients took esomeprazole for 4 to 6 consecutive days, and 11% required medication for 7 to 13 days. Mean antacid use was significantly lower in the esomeprazole group (1.04 tablets/day) compared with the placebo group (0.59 tablets/day). On average, esomeprazole was taken once every 3 days. In an economic analysis on on-demand therapy, Wahlqvist et al [6] evaluated the cost-effectiveness of on-demand therapy in the United Kingdom using clinical data from this and other trials and suggested that on-demand therapy was cost-effective compared with conventional maintenance therapy.

### Combinations of proton-pump inhibitors and $H_2$ -receptor antagonists

Nocturnal reflux may play an important role in the development of complications of reflux disease because natural defense mechanisms are impaired, and acid contact time with the esophageal mucosa can be prolonged. Conventional wisdom argues against the simultaneous administration of PPIs and  $H_2RA$ s because PPIs act at the final point of acid secretion, and blocking the histamine receptor is unlikely to add benefit. Studies have shown, however, that intragastric pH in healthy volunteers and patients with GERD on PPI therapy can decrease to less than 4 at night [7]. Although intragastric pH may decrease to less than 4, nocturnal symptoms are uncommon in patients on PPIs [8]. Studies in human volunteers showed



that the addition of small doses of H<sub>2</sub>RAs at bedtime can prevent the nocturnal decrease in pH in patients taking PPIs [9]. Preliminary data from another study suggest, however, that the effect may be short-lived and that tachyphylaxis may occur within 2 weeks of starting H<sub>2</sub>RA therapy [10]. There are no data on nocturnal symptoms at present and little information on the long-term efficacy of a combination of PPI therapy with H<sub>2</sub>RAs. Further data are awaited on the use of H<sub>2</sub>RAs in combination with PPIs.

### Summary

On-demand therapy with PPIs is a new strategy that has been shown to be effective in patients with nonerosive reflux disease or mild erosive reflux disease. This strategy can reduce the cost of maintenance therapy substantially and is particularly appealing in patients with no evidence of mucosal disease. The long-term efficacy and safety of this form of therapy have not been established. Nocturnal reflux may be important in patients with complicated reflux disease or Barrett's esophagus. Data on combining PPIs with H<sub>2</sub>RAs suggest that nocturnal gastric pH can be controlled by the administration of H<sub>2</sub>RAs at bedtime. There are few data on nocturnal symptoms, and some studies suggest that tachyphylaxis may develop with H<sub>2</sub>RA therapy. More data are required on the clinical effectiveness of combination therapy administered long-term.

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# Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome

M. MICHAEL WOLFE\* and GEORGE SACHS†

\*Section of Gastroenterology, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; and †Division of Gastroenterology, UCLA School of Medicine and West Los Angeles VA Medical Center, Los Angeles, California

One of the hallmarks of the mammalian stomach is its ability to secrete large quantities of concentrated (0.16 mol/L) hydrochloric acid (HCl).<sup>1</sup> Although it is generally assumed that gastric acid and the proteolytic enzyme pepsin are required to initiate digestion, achlorhydric individuals generally do not develop malabsorption unless small bowel bacterial overgrowth is present. It is thus likely that the ability of the stomach to secrete acid evolved primarily from a need to sustain a sterile intragastric milieu. Organisms that possessed the capacity to kill ingested bacteria and other microbes were able to avoid the development of enteric colonization, and thereby ensure both efficient absorption of nutrients and prevention of systemic infections.<sup>1</sup> Nevertheless, when present, gastric acid does play a significant role in protein hydrolysis and other aspects of the digestive process, and under various conditions, acid may play an etiologic role in producing various forms of discomfort and inciting esophageal and gastroduodenal mucosal injury.

The normal human stomach contains approximately 1 billion parietal cells that secrete hydrogen ions into the gastric lumen in response to various physiological stimuli. The generation of H<sup>+</sup> ions is mediated by 3 pathways: neurocrine, paracrine, and endocrine (Figure 1). The principal neurocrine transmitter is acetylcholine, which is released by vagal postganglionic neurons and appears to stimulate H<sup>+</sup> ion generation directly via a parietal cell muscarinic M<sub>3</sub> receptor. Histamine is the primary paracrine transmitter that binds to H<sub>2</sub>-specific receptors on parietal cells. Adenylate cyclase is then activated, leading to an increase in adenosine 3',5'-cyclic monophosphate (cAMP) levels and subsequent generation of H<sup>+</sup> ions. The secretion of gastrin from antral G cells comprises the endocrine pathway and stimulates H<sup>+</sup> ion generation both directly and indirectly, the latter by stimulating histamine secretion from enterochromaffin-like (ECL) cells of the corpus and fundus. Interactions among neurocrine, paracrine, and endocrine pathways are coordinated to promote or inhibit H<sup>+</sup> ion generation. Hista-

mine appears to represent the dominant route, because gastrin stimulates acid secretion principally by promoting histamine release from ECL cells.<sup>2,3</sup> Thus, ECL cells are often referred to as "controller" cells in the process of gastric acid secretion.

A negative feedback loop governs both gastrin release and the return of acid secretion to basal level.<sup>1,4-6</sup> This autoregulatory mechanism prevents postprandial acid hypersecretion. After ingestion of a meal, gastrin release stimulates secretion of gastric acid. The intraluminal pH begins to decrease, which stimulates release of somatostatin from antral D cells, possibly through the activation of calcitonin gene-related peptide (CGRP) neurons.<sup>5,7</sup> Somatostatin then appears to act via a paracrine mechanism to inhibit further release of gastrin from G cells.<sup>8</sup> Somatostatin produced by D cells in the gastric corpus and fundus may also directly inhibit acid secretion from parietal cells and may suppress histamine release from ECL cells (Figure 1).<sup>6,9</sup> Other recent observations indicate that several other neurotransmitters, including vasoactive intestinal peptide (VIP), galanin, and pituitary adenylate cyclase-activating peptide, may play important roles in regulating gastric acid secretion, both directly and indirectly, under physiological conditions.<sup>10</sup>

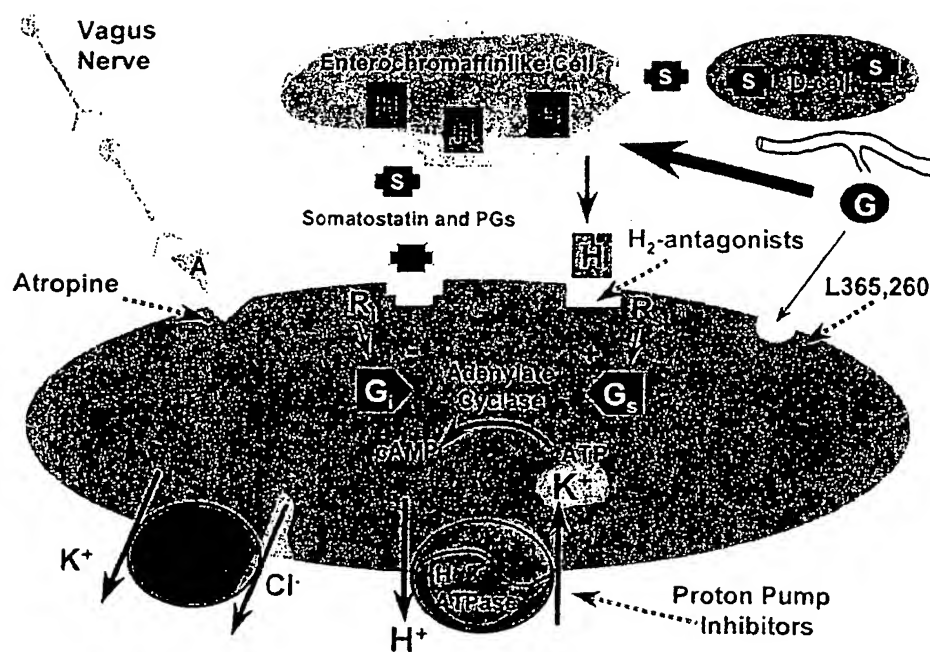
## Pathophysiology of Acid-Related Disorders

### Gastroduodenal (Peptic) Ulcer

The treatment of duodenal ulcer (DU) has served as the basis (correctly or incorrectly) for the management of nearly all acid-related disorders. This supposition in all likelihood contributed to delays in the optimal management of other gastrointestinal (GI) disorders in which

*Abbreviations used in this paper:* DU, duodenal ulcer; ECL, enterochromaffin-like; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GU, gastric ulcer; NCCP, noncardiac chest pain; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

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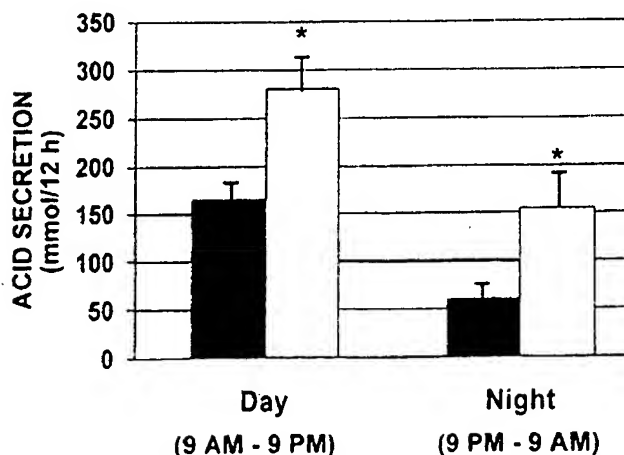
**Figure 1.** Schematic representation of the factors influencing gastric acid secretion by the parietal cell, depicting neurocrine (acetylcholine and other neurotransmitters from vagal efferent neurons), paracrine (somatostatin from D cells and histamine from gastric ECL cells), and endocrine (circulating gastrin) factors. Dashed arrows indicate potential sites of pharmacological inhibition of acid secretion, either via receptor antagonism or via inhibition of  $H^+, K^+$ -ATPase. A, acetylcholine and other neurotransmitters; H, histamine; G, gastrin; L365,260, synthetic gastrin receptor antagonist; PG, prostaglandin; S, somatostatin.

acid plays an etiologic role in producing symptoms and causing mucosal injury, such as gastroesophageal reflux disease (GERD). Although patients with gastric ulcers (GUs) tend to have normal or reduced levels of acid secretion,<sup>1</sup> the average DU patient is an acid hypersecretor. When compared with age-matched controls, DU patients secrete ~70% more acid during the day (meal-stimulated) and about 150% more acid at night (basal secretion) (Figure 2).<sup>11</sup> Postprandial gastric acid secretion is regulated primarily by increases in gastrin expression, which is controlled by a negative feedback loop. Individuals infected with *Helicobacter pylori* have been shown to have a diminished number of somatostatin-secreting D

cells, which decreases the magnitude of the response to luminal acidification.<sup>12-14</sup> Thus, in patients with *H. pylori* infection limited to the antrum, the negative feedback inhibition of gastrin release is attenuated, resulting in higher postprandial gastrin levels and hypersecretion of acid.

Despite the existence of meal-induced hyperchlorhydria in DU patients, the presence of food in the stomach has a buffering effect that may protect the gastroduodenal mucosa from acid-induced injury. However, at night and during other prolonged periods of fasting, acid bathes the "bare" mucosa, and in DU patients, the increase in nocturnal acid secretion magnifies this effect. Duodenal bicarbonate secretion also appears to be impaired in patients with DU,<sup>15</sup> as well as in those infected with *H. pylori*, making the mucosal exposure to acid even greater. These observations, as discussed below, form the rationale for single nocturnal dosing of  $H_2$ -receptor antagonists in the treatment of DU, a mode of therapy that is at least as effective as multiple dosing regimens.

Clearly, factors other than acid and pepsin are involved in the pathogenesis of peptic ulcer disease (PUD), because only 30% of patients with DUs and very few patients with GUs are hyperchlorhydric.<sup>1</sup> The balance between aggressive factors that act to injure the gastroduodenal mucosa and defensive factors that normally protect against corrosive agents is also important. When this delicate balance is disrupted for any reason, mucosal injury may ensue.<sup>1</sup> These defensive properties appear to be mediated to a large extent by endogenous prostaglandins, nitric oxide, and trefoil proteins, and when the



**Figure 2.** Gastric acid secretion during the day and night in patients with DU (n = 8) and in age-matched controls (n = 7). Acid secretion is expressed as the mean  $\pm$  SE in millimoles per 12 hours. \* $P < 0.05$ . Data from Feldman et al.<sup>11</sup>

synthesis of any or all are diminished, the ability of the gastroduodenal mucosa to resist injury is decreased. Thus, even normal rates of acid secretion may be sufficient to injure the mucosa and produce gastroduodenal ulcers. Nevertheless, even in DU patients who are normal secretors of acid, a reduction in the rate of acid secretion is the most efficient means of healing ulcers.<sup>1</sup>

Although a large number of gastroduodenal ulcers are associated with *H. pylori* infection, at least 60% of individuals with complicated ulcers (e.g., hemorrhage or perforation) report the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin.<sup>16</sup> Mucosal injury associated with NSAID use is initiated topically by the acidic nature of NSAIDs.<sup>17</sup> Topical mucosal injury may also occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites.<sup>18,19</sup> Topical injury caused by NSAIDs certainly contributes significantly to the development of gastroduodenal mucosal injury, but the systemic effects of these agents appear to play the predominant role,<sup>17,20,21</sup> largely through the decreased synthesis of mucosal prostaglandins.<sup>22</sup> Avoidance of topical mucosal injury by enteric-coated aspirin preparations<sup>22</sup> or by the parenteral<sup>23</sup> or rectal<sup>24</sup> administration of NSAIDs does not prevent the development of ulcer complications. Moreover, doses of aspirin as low as 10 mg are sufficient to significantly suppress gastric mucosal prostaglandin synthesis.<sup>25</sup> A decrease in the above protective mechanisms normally stimulated by prostaglandins enables endogenous gastric acid to incite mucosal injury.

In recent years, it has become evident that the actual percentage of ulcers associated with *H. pylori* may not be 90%–95% as often reported, but may be as low as 32% in non-referral-based populations.<sup>26</sup> Furthermore, despite the inclination to ascribe the etiology of ulcers in such individuals to NSAIDs, the use of these agents clearly does not account for the balance of the cases. Finally, the vast majority of remaining individuals do not have the Zollinger–Ellison syndrome (ZES) or another unusual cause of gastroduodenal ulcer. Thus, while peptic ulceration involves the participation of several factors, as first stated by Karl Schwarz<sup>27</sup> in 1910: "*Ohne sauren Magensaft, kein peptisches Geschwür*," i.e., "No acid, no ulcer." The erosive properties of acid continue to play a central role in the pathogenesis of gastroduodenal mucosal ulceration, and conversely, acid suppression therapy remains the cornerstone of therapy.

## GERD

Although the principal aggressive factor involved in causing heartburn and the other clinical manifestations

of GERD is the presence of acid in the esophagus, the disorder does not usually result from the hypersecretion of gastric acid.<sup>28</sup> Rather, GERD occurs as a result of several abnormalities in motor function of the lower esophagus and the lower esophageal sphincter (LES). Despite the etiologic role played by these important motor abnormalities, the severity of symptoms, most notably heartburn, and esophageal mucosal injury can be correlated with the total time that the esophageal mucosa is exposed to acid. Gastric acid thus also constitutes a critical element in the pathogenesis of GERD, and acid suppression comprises the principal mechanism for therapy. However, the optimal timing and degree of acid suppression differ significantly in GERD patients compared with the treatment of gastroduodenal ulcer (see below).

## Stress-Related Erosive Syndrome

Many terms have been used to describe this entity, including stress ulcer syndrome, stress gastritis, stress-related mucosal disease, and stress-related erosive syndrome (SRES).<sup>29,30</sup> The principal feature of SRES is its relationship to serious systemic disease, such as sepsis, massive burn injury, head injury associated with increased intracranial pressure, severe trauma, and multiple-system organ failure. A meta-analysis of 2252 patients by Cook et al.<sup>31</sup> identified mechanical ventilation and coagulopathy as the 2 singlemost important risk factors. Although the pathophysiology is multifactorial and definitely includes a component of ischemia, which compromises gastric mucosal integrity, luminal acid plays a dominant role in producing the multiple erosive lesions characteristic of the entity. Fiddian-Green et al.<sup>32</sup> emphasized the importance of H<sup>+</sup> ion back-diffusion by demonstrating a high correlation between the degree of intramural pH and the development of SRES. Furthermore, most, but not all, methods for preventing massive hemorrhage-associated SRES include the alkalinization of gastric contents.<sup>33</sup>

## Pharmacology of Parietal Cell Receptors

The parietal cell possesses a unique morphology that differs markedly between the resting and stimulated states.<sup>1</sup> Mitochondria occupy 34% of its cell volume, indicative of the importance of adenosine triphosphate (ATP) synthesis as an energy source required for the active transport of H<sup>+</sup> ions out of the cell against a 3,000,000:1 ionic gradient. A large percentage of resting cell volume is also occupied by tubulovesicles, which are elongated tubes with smooth surface membranes, and by the

secretory canaliculus, a small invaginated area of the apical membrane. Upon stimulation, which is generally accomplished by eating a meal, the tubulovesicles decrease in number and become transformed into microvilli around the secretory canaliculus, which serves to greatly expand the surface area of the parietal cell in preparation for the secretion of large quantities of HCl. The parietal cell also possesses several different receptors for stimulatory and inhibitory ligands on its basolateral membrane (Figure 1).

### Histamine H<sub>2</sub> Receptor and Its Antagonists

The histamine receptor belongs to a large family of G protein-linked receptors possessing 7 transmembrane domains.<sup>34</sup> Despite the recognition that histamine stimulates gastric acid secretion, it was not until 1966, when Ash and Schild<sup>35</sup> described H<sub>1</sub> and H<sub>2</sub> receptors for histamine, that the possibility of inhibiting acid secretion with histamine antagonists was proposed. In 1970, Black et al.<sup>36</sup> described selective histamine H<sub>2</sub>-receptor inhibition and initiated the search for pharmacological agents that could effectively suppress the secretion of acid. Within 10 years of the release of cimetidine in the United States in 1977, 3 additional H<sub>2</sub>-receptor antagonists—ranitidine, famotidine, and nizatidine—became available for use throughout the world. All 4 drugs (Figure 3) suppress basal and meal-stimulated acid secretion, albeit to a lesser degree than proton pump inhibitors (PPIs) discussed below. Despite similar therapeutic profiles, some differences do exist with regard to the agents' pharmacokinetic properties (Table 1), most of which are clinically insignificant.<sup>37</sup> The elimination of these drugs occurs by a combination of hepatic metabolism and urinary excretion, and although hepatic dysfunction does not alter their pharmacokinetic properties, dose reductions are recommended for all individuals with varying degrees of renal impairment (Table 2).<sup>37</sup> H<sub>2</sub>-receptor antagonists as a class possess an unsurpassed

**Table 1.** Comparison of the Histamine H<sub>2</sub>-Receptor Antagonists

|   | Cimetidine | Ranitidine | Famotidine | Nizatidine |
|---|------------|------------|------------|------------|
| Bioavailability (%)                           | 80         | 50         | 40         | 70         |
| Relative potency                              | 1          | 5-10       | 32         | 5-10       |
| Circulatory t <sub>1/2</sub> (h)              | 1.5-2.3    | 1.6-2.4    | 2.5-4      | 1.1-1.6    |
| Biological t <sub>1/2</sub> (h)               | 6          | 8          | 12         | 8          |
| Relative effect on cytochrome P450 metabolism | 1          | 0.1        | 0          | 0          |

t<sub>1/2</sub>, half-life.

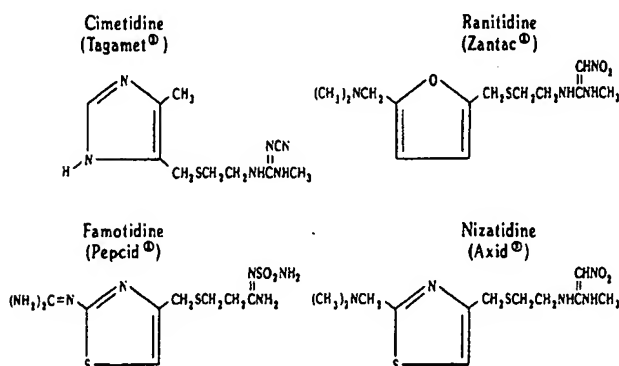
\*Approximate values.

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safety record, and in 1995 became available for use in the United States without prescription.

### Muscarinic Receptor and Its Antagonists

The central nervous system, particularly via the vagus nerve, plays a dominant role in regulating basal acid secretion, as well as the cephalic phase of meal-stimulated acid secretion. Extracts of belladonna were used to treat dyspepsia since the time of the Roman empire, and in the recent past, nonspecific antimuscarinic agents such as atropine and propantheline bromide were used as inhibitors of gastric acid secretion. These drugs were associated with many adverse effects, including drowsiness, dry mouth, blurry vision, and urinary retention, and as a result are rarely used today. To date, however, 5 muscarinic receptors have been subtyped and cloned, and although all are G protein coupled, they signal different intracellular pathways. In vitro characterization of gastric acid secretion has indicated that the parietal cell normally expresses the M<sub>3</sub> subtype.<sup>38</sup> Clinically, the M<sub>1</sub> antagonists, pirenzepine and telenzepine, are effective inhibitors of acid secretion and probably



**Figure 3.** Structure of the 4 H<sub>2</sub>-receptor antagonists in use in the United States.

**Table 2.** Histamine H<sub>2</sub>-Receptor Antagonist Dosing Adjustments With Renal Insufficiency

| Drug       | Creatinine clearance (mL/min) | Dose (mg/day) <sup>a</sup> |
|------------|-------------------------------|----------------------------|
| Cimetidine | >30                           | 800                        |
|            | 15-30                         | 600                        |
|            | <15                           | 400                        |
| Ranitidine | >75                           | 300                        |
|            | 30-75                         | 225                        |
|            | 15-30                         | 150                        |
| Famotidine | <15                           | 75                         |
|            | >75                           | 40                         |
|            | 30-75                         | 30                         |
| Nizatidine | <15                           | 20                         |
|            | >75                           | 10                         |
|            | 30-75                         | 300                        |
| Nizatidine | >75                           | 300                        |
|            | 30-75                         | 225                        |
|            | 15-30                         | 150                        |
| Nizatidine | <15                           | 75                         |
|            | >75                           | 300                        |
|            | 30-75                         | 225                        |
|            | 15-30                         | 150                        |
|            | <15                           | 75                         |

<sup>a</sup>Dosing for gastroduodenal ulcer.

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exert their effect by interaction with a postsynaptic neuronal  $M_1$  receptor.<sup>1</sup> These 2 agents are available in other countries for the treatment of duodenal ulcer, but they have not been approved for use in the United States.

### Gastrin Receptor and Its Antagonists

As stated above, gastrin stimulates acid secretion via an endocrine pathway and induces  $H^+$  ion generation both directly and indirectly. The precise location and density of the gastrin receptor have been subjects of debate and may be somewhat species dependent. Several studies in rats and other rodents have suggested that gastrin stimulates acid secretion by enhancing the release of histamine from ECL cells.<sup>39,40</sup> Conversely, receptors for gastrin receptors on canine parietal cells have been demonstrated by Soll et al.<sup>41</sup> by employing the analogue  $^{125}I$ -[Leu<sup>15</sup>]gastrin, and by Kopin et al.,<sup>42</sup> who cloned and expressed the gastrin receptor from a purified canine parietal cell complementary DNA library. Moreover, single-cell video imaging has provided direct evidence for a functional gastrin receptor on the parietal cells of rats and rabbits.<sup>43</sup>

The gastrin receptor belongs to the above-mentioned family of G protein-linked receptors possessing 7 transmembrane domains.<sup>42</sup> It is closely related to the receptor for cholecystokinin ("CCK-A" or "CCK-1") and is thus often referred to as the "CCK-B" or "CCK-2" receptor. Gastrin-specific receptor antagonists have been developed, which include L365,260 and YM022.<sup>44</sup> The former is a benzodiazepine derivative that was derived from the fungus *Aspergillus alliaceus* and has been demonstrated to effectively antagonize gastrin-stimulated gastric acid secretion.<sup>44</sup> Despite this effect, these antagonists have not been used clinically as inhibitors of acid secretion. However, they may ultimately prove useful in the treatment of panic and anxiety disorders by virtue of binding to gastrin receptors in the brain.<sup>45</sup>

### Miscellaneous Receptors on the Parietal Cell

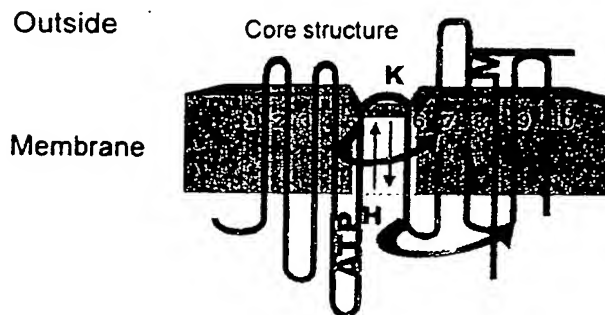
Other receptors on the parietal cell basolateral membrane have been suggested by the ability of various agents to inhibit gastric acid secretion. For example, prostaglandins inhibit  $H^+$  ion generation by binding to their EP3 G protein-linked receptor on the parietal cell, which appears to inhibit adenylate cyclase, and thereby decrease intracellular cAMP generation when activated.<sup>46</sup> As discussed below, the acid-inhibitory properties of prostaglandin analogues such as misoprostol, while not potent, are nevertheless critical for exerting any beneficial clinical effects.<sup>16</sup>

### Parietal Cell $H^+, K^+$ -Adenosine Triphosphatase

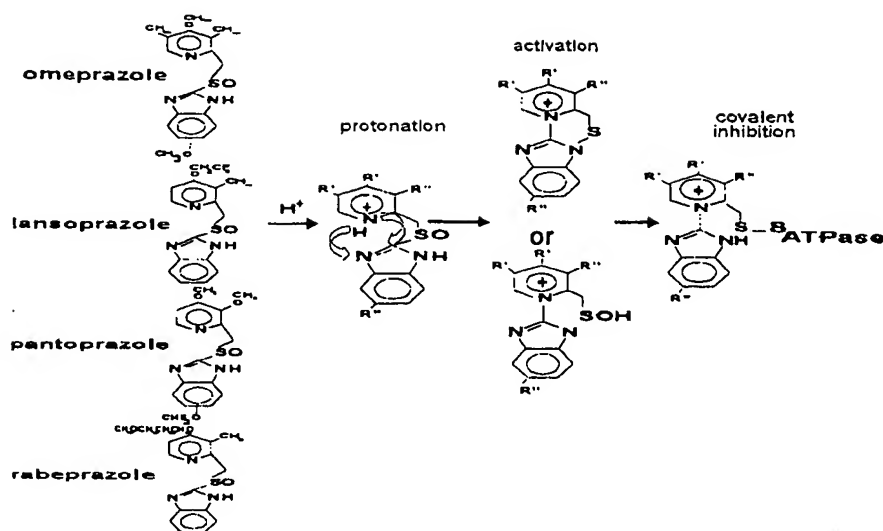
The gastric enzyme  $H^+, K^+$ -adenosine triphosphatase (ATPase) is a member of the family of ion-motive ATPases that includes  $F_1$ , V, and P ATPases. The latter is divided conveniently into  $P_1$  or  $P_2$  types in 1 of 2 ways, either based on the number of transmembrane segments (8 in the case of the  $P_1$  and 10 in the case of the  $P_2$  catalytic subunits) or based on transport of transition metals ( $P_1$ ) or small cations ( $P_2$ ).<sup>47</sup> Within the  $P_2$  family, the gastric  $H^+, K^+$ - and  $Na^+, K^+$ -ATPase isoforms are coexpressed tightly bound to a  $\beta$ -subunit that is smaller than the catalytic or  $\alpha$ -subunit, has most of its sequence presented outside, and is glycosylated to different extents depending on the isoform.<sup>48,49</sup> These latter 2 enzymes are also unique in that they both serve as drug targets, digoxin for congestive heart failure in the case of the  $Na^+, K^+$ -ATPase and substituted pyridyl methylsulfinyl benzimidazoles for acid-related disorders in the case of the  $H^+, K^+$ -ATPase.<sup>50</sup>  $H^+, K^+$ -ATPase consists of 8 transmembrane segments for the catalytic  $\alpha$ -subunit and 1 transmembrane segment for the  $\beta$ -subunit (Figure 4).<sup>51,52</sup>

### Inhibition of Acid Secretion

The recognition that the ATPase was the final step of acid secretion has resulted in the development of a class of drugs, the PPIs, that are targeted toward this enzyme. They all share a common structural motif (Figure 5), a substituted pyridylmethylsulfinyl benzimidazole, but vary in terms of their substitutions. They also share common inhibitory mechanisms and are all weak protonatable pyridines, with a  $pK_a$  of  $\sim 4.0$  for omeprazole, lansoprazole, and pantoprazole, and  $\sim 5.0$  for rabeprazole. They thus accumulate selectively in the acid space of the secreting parietal cell. Within that space or on the surface



**Figure 4.** A model of the 2-dimensional arrangement of the gastric  $H^+, K^+$ -ATPase subunits. The core structure of this  $P_2$ -type ATPase consists of the first 6 membrane segments, arranged as helices with the possible exception of the cytoplasmic end of M6. Cross-linking and column chromatography of tryptic fragments has shown an association between M5 and M7, and M6 and M9 (curved arrows). The major high-affinity interaction with the  $\beta$ -subunit is with the beginning of M8.



**Figure 5.** Structure and reaction pathways of the 4 PPIs in use in the United States. All are ampholytic weak bases and accumulate as prodrugs in the secretory canaliculus of the actively secreting parietal cell. They are all acid-catalyzed to a reactive thiophilic species whereby the pyridine N reacts with the 2C of the benzimidazole to form a sulfenic acid (below), which, while in solution, reacts further to form a sulfenamide (above). The respective sulfenamides then react with available cysteines on the luminal surface of the enzyme; cys 813 is common to all the PPIs and crucial for enzyme inhibition. Cys 892 reacts with omeprazole, lansoprazole, and rabeprazole; cys 321 with lansoprazole; and cys 822 with pantoprazole.<sup>54</sup>

of the enzyme, they undergo an acid-catalyzed conversion to a reactive species, the thiophilic sulfenamide or sulfenic acid, which are permanent cations. The rate of conversion varies among the compounds and is a function of their  $pK_a$  and other structural features: rabeprazole > omeprazole = lansoprazole > pantoprazole.<sup>53,54</sup> The reactive species reacts with cysteine residues available from the external surface of the enzyme that faces the lumen of the secretory space of the parietal cell, resulting in covalent inhibition of the enzyme by disulfide bond formation. The cysteine residue that is critical for inhibition is cys 813 in the catalytic subunit of the  $H^+$ ,  $K^+$ -ATPase, strategically located in the M5/M6 sector of the enzyme, which is intimately involved in the transport process.

Because all the PPIs require accumulation and acid activation, their onset of inhibition is delayed, and because they also form a covalent derivative, the restoration of acid secretion is likewise delayed, depending on the turnover of the pump protein and the biological reversibility of the disulfide bond. Therefore, 24–48 hours are necessary for maximal acid secretory capacity to be restored. Different doses of these drugs are recommended, but at equivalent doses, these agents are remarkably similar when used in the treatment of acid-related disorders (Table 3).<sup>55</sup>

The PPIs are without question the most potent inhibitors of gastric acid secretion available. However, because they are most effective when the parietal cell is stimulated to secrete acid in response to a meal, these

drugs should *only* be taken before or with a meal and should *not* be used in conjunction with  $H_2$ -receptor antagonists, prostaglandins, or other antisecretory agents (Table 3). Animal studies have demonstrated that the concomitant administration of PPIs and other antisecretory agents will markedly reduce the acid-inhibitory effects of the PPI.<sup>56</sup> Because acid secretion must be stimulated for maximum efficacy, PPIs are administered before the first meal of the day (Table 3). Moreover, in

**Table 3.** Helpful Facts on the Use of PPIs

|   |
|---|
| PPIs are prodrugs that require activation to their active moiety (thiophilic sulfenamide)   |
| $pK_a$ of PPIs: ~4 for omeprazole, lansoprazole, and pantoprazole; ~5 for rabeprazole   |
| All PPIs are activated when regional pH decreases below their respective $pK_a$   |
| Achieved almost exclusively in parietal cell secretory canaliculus  |
| Achieved optimally when parietal cell is activated, i.e., after meals   |
| Most effective after a prolonged fast, when a large amount of inactive $H^+$ , $K^+$ -ATPase present is in secretory canaliculus, i.e., after breakfast |
| Clinical use  |
| Steady state not achieved for several days  |
| Thus often helpful to administer twice daily for the first 2–3 days of therapy  |
| Also likely not to be consistently clinically effective when taken sporadically   |
| First dose should be taken before breakfast   |
| Second dose, if used, should be taken before evening meal   |
| Do not administer concomitantly with $H_2$ -receptor antagonists or prostaglandins  |
| Safety: toxicity seems to be gastrin-related and is probably species specific   |



most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition. A second dose, if required, should be administered before the evening meal.

During meals, however, neither all parietal cells nor all proton pumps are active. The initial dose of the PPI will thus inhibit only activated  $H^+$ ,  $K^+$ -ATPase present in the canalicular membrane.<sup>56</sup> As inactive enzyme is recruited into the secretory canaliculus, acid secretion will resume, albeit at a reduced level. After a second dose, more enzyme will have been recruited and subsequently inhibited, and after a third dose, additional recruitment and further acid inhibition may be expected. Once-daily PPI dosing results in 66% steady-state inhibition of maximal acid output after 5 days, and the initial use of twice-daily dosing (for the first 2–3 days) may thus be helpful in achieving more rapid inhibition of gastric acid secretion.<sup>55</sup> Based on these pharmacokinetic properties, the occasional use of a PPI taken on an "as-needed" basis would not be expected to provide adequate acid inhibition and would be unlikely to produce a consistent or satisfactory clinical response.

### Safety Issues

The safety profile of the PPIs is similar to that of  $H_2$ -receptor antagonists. Although headache and diarrhea are occasionally reported, serious adverse reactions to these agents are rare and generally not well documented. Initial concern was expressed when PPIs were introduced as a result of their ability to precipitate ECL cell hyperplasia and subsequent gastric carcinoid tumors in rats when given at high doses. This trophic effect occurs as a result of interruption of the negative feedback mechanism for acid secretion, which induces an increase in antral gastrin gene expression.<sup>1,4–6</sup> However, these drugs have been used for nearly 15 years in Europe and for 10 years in the United States with no discernible increase in the incidence of carcinoid tumors. The reasons for such interspecies differences are not entirely evident, but are probably related in part to a lower mucosal ECL cell density and a considerably less pronounced increase in circulating gastrin in humans compared with rodents in response to antisecretory medications. One area of theoretical concern that has not been completely resolved is the possible effect of gastrin and its precursor proghormone on promoting the growth of colonic neoplasms.

An area of controversy has been the need to monitor serum gastrin concentrations in persons on long-term PPI therapy. In general, laboratory and other testing should be performed only if the treatment plan will be dependent on their results. Long-term PPI treatment is used most commonly in patients with GERD, many of

whom have significant symptoms and mucosal injury. The sequelae of GERD are serious and real, whereas the effects of hypergastrinemia, which occurs in only ~5% of individuals receiving long-term PPI therapy, are theoretical. Therefore, in situations in which the hypothetical risk of the PPI is clearly outweighed by the benefits offered by potent acid suppression, serum gastrin measurements should not be performed.<sup>57</sup>

## Treatment of Acid-Related Disorders

### Acute Gastroduodenal Ulcer

The treatment of ulcer disease has changed dramatically since the discovery that the probability of ulcer recurrence decreases significantly after successful eradication of *H. pylori* infection, compared with annual recurrence rates of 50%–80% when antisecretory therapy alone is used.<sup>58,59</sup> Thus, a determination of *H. pylori* infection in a patient with gastroduodenal ulcer is critical for the appropriate management of this disease. If a patient is not infected with *H. pylori*, an alternative etiology must be sought, such as NSAID use, hypersecretory states, or one of the other less common causes of ulcer disease, such as Crohn's disease, vascular insufficiency, viral infection, radiation therapy, and cancer chemotherapy. Regardless of the etiology, however, the inhibition of gastric acid secretion continues to play a prominent role in the management of acute gastroduodenal ulcer.

Some differences do exist between DUs and GUs proximal to the prepyloric region of the stomach. Most previous studies have assessed the effects of acid suppression on duodenal and pyloric channel ulcers and antral ulcers within 2–3 cm of the pylorus, but few have actually evaluated the healing of more proximal GUs. Although gastric acid secretion is generally lower than normal in patients with more proximal disease,<sup>1</sup> these latter ulcers usually do heal in response to acid suppression, although the total duration of therapy is often prolonged.

In general, a dynamic relationship exists between the healing of DU and the inhibition of intragastric acidity. Important parameters that determine the effect of antisecretory therapy include the degree of suppression of intragastric acidity, the length of acid inhibition over a 24-hour period, and the duration of antisecretory treatment. For example, Burget et al.<sup>60</sup> showed that if intragastric pH is maintained above 3.0 for a period of 18–20 hours per day, DU healing approximates 100% at 4 weeks. As discussed below, the DU healing rate at 4 weeks is also directly proportional to the degree of the reduction of nocturnal acidity.<sup>61</sup>



**Table 4.** Current Recommendations for Treatment of Gastroduodenal Ulcers

|   |  |
|---|--|
| <b>Active ulcer</b>                                   |  |
| H <sub>2</sub> -receptor antagonists                  |  |
| Cimetidine 800 mg                                     |  |
| Ranitidine/nizatidine 300 mg                          |  |
| Famotidine 40 mg                                      |  |
| All administered between the evening meal and bedtime |  |
| <b>PPIs</b>   |  |
| Omeprazole 20 mg                                      |  |
| Lansoprazole 30 mg                                    |  |
| Rabeprazole 20 mg                                     |  |
| Pantoprazole 40 mg                                    |  |
| All administered daily before breakfast               |  |
| <b>Maintenance therapy</b>                            |  |
| H <sub>2</sub> -receptor antagonists                  |  |
| Cimetidine 400 mg                                     |  |
| Ranitidine/nizatidine 150 mg                          |  |
| Famotidine 20 mg                                      |  |
| All administered between the evening meal and bedtime |  |
| <b>PPIs</b>   |  |
| As above  |  |
| <b>Prevention of NSAID-induced ulcers</b>             |  |
| Misoprostol   |  |
| At least 200 µg 3 times/day                           |  |
| <b>PPIs</b>   |  |
| As above  |  |

NOTE. In general, duodenal ulcers should be treated for 4 weeks and gastric ulcers for 8 weeks.

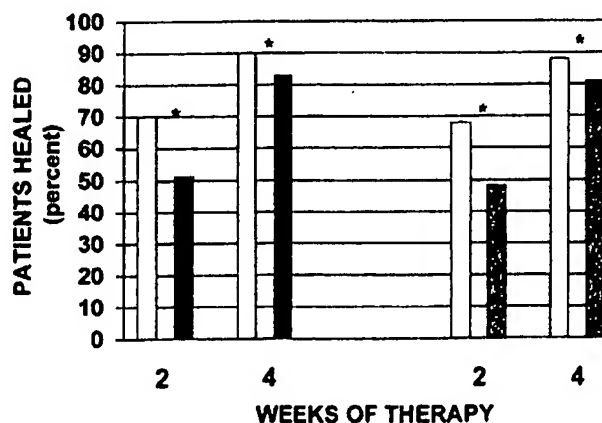
**Antacids.** In a landmark controlled, double-blind study in 1977, Peterson et al.<sup>62</sup> showed that antacids were superior to placebo in healing DU, although (contrary to prevailing opinions) no difference in symptom relief was detected. However, because of the need to take these drugs at least 4, and up to 7, times every day, antacids are rarely used presently in the healing of gastroduodenal ulcers.

**H<sub>2</sub>-receptor antagonists.** These agents (Figure 3) are specific antagonists that inhibit gastric acid secretion competitively and reversibly by blocking the histamine receptor on the parietal cell basolateral membrane. They only partially inhibit acid secretion stimulated by gastrin and are more effective in suppressing intragastric acidity during periods of basal acid secretion. However, DU healing is directly proportional to the degree of the reduction of nocturnal acidity, and because the longest period of basal acid secretion occurs during the night,<sup>61</sup> the optimal time for dosing H<sub>2</sub>-antagonists in the treatment of DU is between the evening meal and bedtime (Table 4). These drugs promote healing in ~70%–80% of patients after 4–6 weeks compared with placebo healing rates of 20%–45%.

Reports in the literature are conflicting regarding the superiority of one H<sub>2</sub>-antagonist over another in healing DUs. McIsaac et al.<sup>63</sup> performed a meta-analysis of 44 clinical trials involving more than 4300 patients to compare DU healing with 4 weeks of ranitidine, 150 mg

twice daily, and cimetidine, 400 mg twice daily or 1 g/day. They found a significant difference between the 2 agents, with overall healing 7% greater in the ranitidine group. However, multidose regimens have been largely replaced by a single evening-dose regime (with an equivalent total daily dose), which takes advantage of the observation that ulcer healing is proportional to the effectiveness of nocturnal acid secretion. In a large American multicenter trial, Gitlin et al.<sup>64</sup> found that 40 mg famotidine twice daily was equivalent to 40 mg of the drug given only once at bedtime in promoting DU healing. In several subsequent comparative trials, 40 mg famotidine and 300 mg nizatidine at bedtime have been found to have an effect similar to ranitidine in healing both DU and GU, with healing of 55%–65% of GU and 73%–75% of DU at 4 weeks.<sup>65,66</sup> Thus, as stated above, it is now recommended that all H<sub>2</sub>-receptor antagonists be administered between the evening meal and bedtime (Table 4) in the treatment of gastroduodenal ulcer. It also appears reasonable to recommend 4 and 8 weeks of therapy for acute DU and GU, respectively.

**PPIs.** As discussed below, in addition to their use in the treatment of gastroduodenal ulcers caused by *H. pylori*, PPIs are the agent of choice for the treatment of ZES and for healing ulcers associated with the use of NSAIDs. PPIs appear to heal gastroduodenal ulcers more rapidly than H<sub>2</sub>-receptor antagonists. In a meta-analysis comparing the healing of DU, Holt and Cowden<sup>67</sup> reported that omeprazole, 20 mg every morning for 4 weeks, was superior to both 300 mg ranitidine and 800 mg cimetidine, both administered at bedtime (Figure 6). Similarly, in another meta-analysis, Poynard et al.<sup>68</sup> found that lansoprazole, 30 mg every morning, healed significantly more ulcers than 300 mg ranitidine and 40 mg famotidine, both administered at bedtime. The



**Figure 6.** Meta-analysis comparing duodenal ulcer healing at 2 and 4 weeks with 800 mg cimetidine (□) or 300 mg ranitidine (■), both administered at bedtime, with 20 mg omeprazole daily (▨). \**P* < 0.001. Data from Holt and Howden.<sup>67</sup>

pooled healing rates were 60% and 85% for lansoprazole at 2 and 4 weeks, respectively; the corresponding figures for the H<sub>2</sub>-antagonists were 40% and 75%.<sup>68</sup> Rabeprazole<sup>69</sup> and pantoprazole<sup>70</sup> have also demonstrated superior and accelerated DU healing compared with H<sub>2</sub>-receptor antagonists. PPIs also appear to heal GUs more rapidly and at a greater rate than H<sub>2</sub>-blockers. For example, Bader and Delchier<sup>70</sup> reported that pantoprazole healed 32% and 15% more GUs at 4 and 8 weeks, respectively, than ranitidine. While clearly more effective, as will be discussed below, the margin of benefit conferred by PPIs over H<sub>2</sub>-antagonists in the healing of ulcers is far smaller than the advantage offered by these agents in the treatment of GERD. Moreover, like the H<sub>2</sub>-blockers, the optimal duration of therapy with PPIs should be 4 and 8 weeks of therapy for acute DU and GU, respectively. The dosing of PPIs in the treatment of gastroduodenal ulcer is summarized in Table 4.

In summary, nearly all peptic ulcers will eventually heal, as evident by the placebo responses in the above-mentioned studies. Antisecretory therapy accelerates the healing process and allows for more rapid relief of symptoms. Antacids, H<sub>2</sub>-receptor antagonists, and PPIs have similar healing rates when given for at least 4 weeks, although the latter agents appear to heal ulcers more rapidly and to a greater extent than the others. Moreover, because PPIs are commonly used in *H. pylori* eradication regimens and because they heal gastroduodenal ulcers in patients continuing NSAID use, they have become, and will likely remain, the mainstay of therapy for healing gastroduodenal ulcers.

### The Role of Maintenance Therapy in Gastroduodenal Ulcer

The natural history of PUD has changed significantly with the recognition that eradication of *H. pylori* infection in DU patients greatly diminishes the relapse rate. Graham et al.<sup>71</sup> showed that after a median follow-up of 38 weeks, only 12% of patients who underwent *H. pylori* eradication relapsed, compared with 95% of patients who received H<sub>2</sub>-receptor antagonists alone. Other studies report similar relapse rates after *H. pylori* therapy, so that the maxim "once an ulcer, always an ulcer" no longer holds true.

Accordingly, the role of maintenance antisecretory therapy has changed in recent years. Before embarking on long-term therapy, careful attention must be paid to the elimination of the most important risk factors for ulcer recurrence: *H. pylori* infection and NSAID use. Several studies have demonstrated the cost-effectiveness of *H. pylori* eradication compared with maintenance antisecretory therapy, which may cost up to \$1200 per year.<sup>72</sup> In

general, only high-risk ulcer patients should be considered as candidates for maintenance antisecretory therapy. This group includes patients with a history of ulcer complications, those who have frequent recurrences, those who are *H. pylori* negative, and those who fail to clear *H. pylori* infection despite appropriate therapy. However, even patients who have had a complicated ulcer may not require maintenance therapy, provided *H. pylori* infection is cured.<sup>73,74</sup> Maintenance therapy regimens include an H<sub>2</sub>-receptor antagonist administered at bedtime at one half the dose required for initial healing or a PPI taken before breakfast (Table 4).

### Role of Acid Inhibition in Healing NSAID-Induced Gastroduodenal Ulcers

The optimal treatment for patients with NSAID-induced gastroduodenal ulcers is the discontinuation of any potentially aggravating factors. If NSAID use must be continued, however, the capacity to heal ulcers varies among the various antisecretory agents.

**H<sub>2</sub>-receptor antagonists.** Several open, uncontrolled, nonrandomized studies<sup>75</sup> and prospective, randomized studies<sup>76</sup> have suggested that treatment with conventional doses of H<sub>2</sub>-receptor antagonists for 6–12 weeks results in healing of ~75% of GUs and 85% of DUs despite the continued use of NSAIDs. When NSAID use is continued, healing appears to be delayed and is largely dependent on the initial ulcer size. O'Laughlin et al.<sup>77</sup> reported a 90% healing rate of small GUs (<5 mm in diameter) after an 8-week course of cimetidine treatment, while only 25% of ulcers >5 mm in diameter healed.

**PPIs.** Recently, Hawkey et al.<sup>78</sup> compared the capacity of misoprostol (200 µm 4 times daily) and omeprazole (20 mg or 40 mg daily) to heal gastroduodenal ulcers in patients continuing NSAID therapy (OMNIUM Study). After 8 weeks of therapy, omeprazole at both doses healed 89% of the DUs, whereas only 77% of DUs in those receiving misoprostol were healed. GU healing was detected in 80%, 87%, and 73% of those receiving 40 mg omeprazole, 20 mg omeprazole, and misoprostol, respectively.<sup>78</sup>

In a recent multicenter trial by Yeomans et al. (ASTRONAUT Study)<sup>79</sup> in a group of 541 patients, the superiority of omeprazole over ranitidine in treatment of NSAID-related gastroduodenal ulcers was demonstrated. Ulcer healing rates at 8 weeks were 79%, 80%, and 63% in those receiving 40 mg omeprazole, 20 mg omeprazole, and 150 mg ranitidine twice daily, respectively. Another study by Agrawal et al.<sup>80</sup> compared the efficacy of lansoprazole and ranitidine in healing of GUs in patients continuing NSAID therapy. After 8 weeks, ulcers were healed in 57% of individuals receiving 150 mg ranitidine

twice daily, while healing rates were 73% and 75% in those treated with 15 and 30 mg lansoprazole (each once daily), respectively. These observations indicate that PPIs have the capacity to heal gastroduodenal ulcers at an accelerated rate whether or not NSAID use is continued. Although ulcer healing is possible with H<sub>2</sub>-receptor antagonists and antisecretory doses of misoprostol, the above studies indicate that the more potent inhibition of gastric acid secretion provided by PPIs enhances their healing properties (Table 4).

### Prophylaxis of NSAID-Associated Gastroduodenal Ulcers

Because of the number and serious nature of NSAID-related GI complications, recent efforts have been directed at the prevention of mucosal injury induced by NSAIDs. Although the optimal means of minimizing this risk is to avoid NSAIDs and substitute with a less toxic agent, NSAID use is commonly preferred. Two strategies have thus been used to prevent ulcers: the use of concomitant medication and the development of safer anti-inflammatory agents, such as the cyclooxygenase 2-specific inhibitors and nitric oxide-releasing NSAIDs. The use of these latter agents has been reviewed recently<sup>16,81</sup> and will not be discussed below. Because dyspeptic symptoms are not a reliable warning sign for the development of serious NSAID-related mucosal injury,<sup>16</sup> it is important to identify patients who are more likely to suffer adverse consequences with NSAID therapy. Advanced age has been consistently found to constitute one of the primary risk factors for adverse GI events and appears to increase in a linear fashion.<sup>16</sup> Contrary to previous reports suggesting adaptation with time, recent studies indicate that the risk of NSAID-associated GI hemorrhage remains constant over an extended period of observation.<sup>82</sup> Other risk factors include high NSAID doses, prior history of gastroduodenal ulcer and gastrointestinal bleeding, use of concomitant corticosteroids, significant comorbid conditions, and coadministration of anticoagulants.<sup>16</sup> However, many of these studies are based on univariate analysis and do not consider the interactions among multiple factors and comorbidities.

The identification of *H. pylori* as an etiologic factor in the development of peptic ulcer has raised the question of a possible synergistic relationship between the presence of this organism and NSAID use in the development of gastroduodenal mucosal injury. Most,<sup>83–86</sup> but not all,<sup>87,88</sup> studies have found these 2 risk factors to be independent. For example, Chan et al.<sup>88</sup> found that eradication of *H. pylori* using a regimen that included bismuth subcitrate significantly decreased the occurrence of ulcers associated with the use of naproxen. In this study, ulcers developed

in 26% of *H. pylori*-infected individuals but in only 7% of persons successfully treated with antimicrobial therapy. While provocative, the inclusion of bismuth in the drug regimen conferred a level of ambiguity to this study because of the ability of bismuth to accumulate in the gastric mucosa and stimulate prostaglandin synthesis.<sup>89</sup> Most recently, Hawkey et al.<sup>90</sup> randomized 285 patients with current or previous ulcers receiving NSAIDs to therapy with omeprazole, clarithromycin, and amoxicillin or omeprazole alone and found that although *H. pylori* eradication did not affect the rate of ulcer recurrence, gastric ulcer healing was *impaired* in those individuals successfully treated. It thus appears that *H. pylori* infection increases the risk of gastroduodenal injury associated with NSAID use only minimally, if at all.<sup>16</sup>

**H<sub>2</sub>-receptor antagonists.** Two large placebo-controlled, prospective trials investigated the protective effect of ranitidine in arthritis patients receiving concomitant NSAID therapy.<sup>91,92</sup> Ranitidine, 150 mg twice per day, proved to be effective in preventing DUs, with rates of 0% and 1.5% in the 2 studies, compared with 8% in placebo-treated patients. In contrast, ranitidine at this dose was ineffective in preventing GUs in both studies. Taha et al.<sup>93</sup> recently reported a beneficial effect of high-dose famotidine (40 mg twice per day) in preventing both gastric and DUs in arthritis patients receiving NSAIDs for 24 weeks. Although symptomatic relief was also observed in the group randomized to famotidine, the beneficial effect, although statistically significant, was modest, and the cost associated with such doses of H<sub>2</sub>-receptor antagonists is considerable. Thus, the use of H<sub>2</sub>-receptor antagonists in the prevention of NSAID-associated ulcers cannot be recommended.

**PPIs.** In addition to examining ulcer healing, the recent ASTRONAUT study also compared omeprazole and ranitidine in the prevention of recurrent gastroduodenal ulcer in a large number of arthritic individuals in whom ulcers had healed and NSAID therapy was continued. A group of 432 patients was randomly assigned to treatment with either 20 mg omeprazole once daily or 150 mg ranitidine twice daily.<sup>79</sup> At the end of 6 months, 16.3% and 4.2% of those given ranitidine developed gastric and DUs, respectively, while only 5.2% developed a GU and 0.5% a DU in the omeprazole group.<sup>79</sup>

In the recent OMNIUM study, the capacity of omeprazole and misoprostol in preventing ulcer recurrence was compared in arthritic individuals continuing NSAID therapy.<sup>78</sup> In this double-blind, placebo-controlled trial, 732 patients in whom ulcers had healed were randomized to receive either placebo, 20 mg of omeprazole once daily, or 200 µm of misoprostol twice per day as maintenance therapy. After 6 months, DUs were detected in 12% and

10% of those treated with placebo and misoprostol, respectively, while only 3% of those treated with omeprazole developed a DU. Gastric ulcer relapse occurred in 32%, 10%, and 13% of the individuals receiving placebo, misoprostol, and omeprazole, respectively.<sup>78</sup> These studies suggest that PPIs are superior to H<sub>2</sub>-receptor antagonists in maintaining patients in remission during continued NSAID use,<sup>16,94</sup> as well as in improving dyspeptic symptoms associated with the use of NSAIDs.

**Prostaglandins.** As discussed above, although not potent antisecretory agents, the acid-inhibitory properties of misoprostol appear to be critical for exerting its beneficial clinical effects. In their initial study, Graham et al.<sup>95</sup> reported that the prevalence of GUs in osteoarthritis patients who were receiving NSAIDs was 1.4% in those concomitantly taking 200  $\mu$ m misoprostol 4 times daily, 5.6% receiving 100  $\mu$ m misoprostol 4 times daily, and 21.7% receiving placebo. The efficacy of misoprostol in DU prophylaxis was confirmed in another study by Graham et al.<sup>96</sup> In this group of 638 patients, misoprostol significantly reduced the incidence of DUs from 4.6% in those taking placebo to 0.6% in those receiving 200  $\mu$ m misoprostol 4 times daily. Because of the dose-dependent adverse effects of this agent, Raskin et al.<sup>97</sup> conducted a study to evaluate 3 different regimens (200  $\mu$ m twice, 3 times, and 4 times daily). Their study indicated that, although lower doses of misoprostol are better tolerated, the drug must be taken at least 3 times a day to provide significant prophylaxis for NSAID-induced GUs. Finally, Silverstein et al.<sup>98</sup> conducted the Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) trial and observed a 40% reduction in overall complications from NSAID-associated ulcers in individuals taking 200  $\mu$ m misoprostol 4 times per day.<sup>98</sup>

Despite being a highly effective form of therapy for preventing NSAID-induced ulcers and the only drug approved by the Food and Drug Administration (FDA) for prophylaxis against NSAID-related gastroduodenal ulcers, misoprostol is associated with a significant number of adverse effects, including dose-related diarrhea and spontaneous abortion. Presently, it thus appears that after an NSAID-related gastroduodenal ulcer is healed and it is determined that NSAID use must be continued, recurrent ulceration may be prevented either by the use of a cyclooxygenase 2-specific inhibitor, such as celecoxib or rofecoxib, or concomitant administration of misoprostol (at least 200  $\mu$ m 3 times daily) or a PPI (Table 4).<sup>16,81</sup> However, it must be stressed that, despite the marked efficacy of PPIs in improving dyspeptic symptoms and preventing endoscopic ulcers caused by NSAID use,<sup>16,81,94</sup> prospective clinical outcome analyses have not yet been performed to assess the ability of PPIs to prevent

NSAID-related ulcer complications. Likewise, studies aimed at determining the most cost-effective means of approaching the significant issue of NSAID-related GI toxicity have not yet been performed.

## ZES

Although concern for patients with ZES initially revolved around massive hyperchlorhydria and virulent peptic ulceration, the availability of potent inhibitors of acid secretion refocused attention on the malignant potential of the gastrinoma.<sup>99,100</sup> The goal of therapy in patients with ZES is surgical extirpation of all tumor, which is possible in ~50% of individuals with sporadic gastrinoma. A recent study by Norton et al.<sup>99</sup> confirmed the inability to successfully maintain individuals with familial forms (multiple endocrine neoplasia type I) in a disease-free state for prolonged periods. These patients require potent acid suppression for an indefinite period. Moreover, all patients with ZES, whether sporadic or familial, require antisecretory therapy after the diagnosis is established and during initial evaluation as attempts are made to localize the gastrinoma.

Patients with ZES should be treated initially with a PPI, using twice the dose normally employed to treat gastroduodenal ulcers associated with *H. pylori* infection or NSAID use (e.g., 40 mg omeprazole or 40 mg rabeprazole, 60 mg lansoprazole, or 80 mg pantoprazole, all administered before breakfast).<sup>100</sup> The relief of epigastric pain does not reliably predict the absence of mucosal injury,<sup>101</sup> although the relief of all symptoms associated with ZES, including heartburn and diarrhea, is desirable. The only parameter to reliably predict gastroduodenal mucosal injury is the level of acid inhibition. After a steady state has been achieved, basal acid output should be measured 1 hour before the next dose of the PPI is to be administered. The goal of therapy is not achlorhydria, but rather a basal acid output of 1–10 mmol/h.<sup>101</sup> If complete inhibition of acid secretion is evident, the PPI dose should be decreased by 50% and the patient reassessed. If the basal acid output is >10 mmol/h, the dose should be increased incrementally, and for doses >60 mg of omeprazole (or an equivalent dose for the other PPIs), the PPI should be divided and one half given before breakfast and one half before dinner. Patients should be evaluated periodically (every 6–12 months) and dose adjustments made accordingly. In contrast to the H<sub>2</sub>-receptor antagonists, which are now rarely used for the treatment of the ZES because of tachyphylaxis associated with their prolonged use, the need to increase the PPI dose is necessary in only ~10% of ZES patients.<sup>101</sup>

## GERD

Therapy for GERD can be approached in 2 different fashions. The correction of the mechanisms involved in the pathogenesis of GERD includes a decrease in the frequency of transient LES relaxations and an improvement of esophageal clearance to minimize the exposure of the esophagus to acidic gastric contents. The more commonly used approach, however, employs the neutralization or suppression of intragastric acidity, whereby, despite the continued reflux of gastric contents into the esophagus, the refluxate is rendered nonirritating to the esophageal mucosa (Table 5). This approach not only provides symptomatic relief, but also treats and prevents mucosal injury.

**Antacids.** Antacids have been used since the time of the ancient Greeks, who used coral powder (containing calcium carbonate) to treat various digestive maladies. Before the introduction of cimetidine in the mid-1970s, they comprised the mainstay of therapy for GERD. Although a few old studies compared antacids with cimetidine in the treatment of esophagitis,<sup>102,103</sup> these drugs are now used exclusively to treat mild episodic heartburn and are rarely prescribed. When used by individuals for the treatment of heartburn, they offer the advantage of prompt, although often unsustained, relief.

**Histamine H<sub>2</sub>-receptor antagonists.** The H<sub>2</sub>-receptor antagonists are used extensively for GERD, both in over-the-counter and prescription formulations. Early studies of the efficacy of these drugs were disappointing, largely because they were performed using doses commonly employed to treat PUD. It is now recognized that GERD requires higher doses of H<sub>2</sub>-antagonists to effectively treat this disorder. A randomized, controlled trial of cimetidine, 800 mg twice daily for 12 weeks, showed

symptom relief and mucosal healing in 67% of patients, compared with 36% in the placebo arm.<sup>104</sup> Similar studies of famotidine showed 12-week healing rates of 75% for dosing 20 mg twice daily and 66% for dosing 40 mg at bedtime.<sup>105</sup> Other studies show comparable results, with 50%–75% rates of symptom relief and healing. The rates of healing are clearly related to the initial severity of esophagitis, with rates for grade I–II esophagitis approaching 80%, and rates of only 30%–50% with grade III–IV disease.<sup>106</sup> The timing of drug administration is also important. In patients with erosive GERD, most reflux episodes occur between the evening meal and midnight, and in mild GERD, nocturnal acid suppression may be as effective as multiple daily doses. Studies comparing nocturnal with twice-daily dosing show 80%–90% healing rates for grade I disease, 60%–70% for grade II, and 40%–50% for grade III.<sup>105,107,108</sup> Thus, patients with grade I esophagitis may benefit from once-daily dosing after dinner or bedtime, but patients with higher grades of disease will generally require multiple doses per day. In all cases, however, individualization of therapy must be considered.

**PPIs.** Numerous studies have documented the efficacy of PPIs in controlling GERD symptoms and healing esophagitis. Pooled data from 3 studies including 653 patients treated with lansoprazole, 30 mg daily, in patients with grade II or worse esophagitis showed 80%–90% healing at 4 weeks and 92% healing at 8 weeks.<sup>109–111</sup> Comparative trials of PPIs and H<sub>2</sub>-antagonists show a clear advantage with the former agents. One trial comparing lansoprazole, 30 mg daily, and ranitidine, 300 mg twice daily, in patients with moderate-to-severe erosive GERD showed 91% healing in 8 weeks with lansoprazole compared with 66% healing for ranitidine.<sup>112</sup> PPIs are also effective in patients with GERD unresponsive to high-dose H<sub>2</sub>-blocker therapy. In patients refractory to cimetidine, 800 mg 4 times daily, or ranitidine, 300 mg 3 times daily, therapy with 40 mg omeprazole in the morning healed esophagitis in 91% of patients studied.<sup>113</sup>

In general, standard doses of PPIs (20 mg omeprazole, 30 mg lansoprazole, 20 mg rabeprazole, or 40 mg pantoprazole, all administered before breakfast) will relieve symptoms and heal esophagitis in approximately 85%–90% of cases (Table 5). In a large meta-analysis, Chiba et al.<sup>114</sup> clearly demonstrated the superiority of PPIs over H<sub>2</sub>-receptor antagonists in both relieving symptoms and in healing esophagitis. In nonresponders, a careful history regarding the timing of PPI administration should be obtained. As stated above, the optimal time is immediately before breakfast. Once the correct timing is established, a second dose of the PPI (before the

**Table 5.** Antisecretory Drug Regimens for Treatment of GERD

|   |   |
|---|---|
| <b>H<sub>2</sub>-receptor antagonists</b> |   |
| <b>Nonerosive GERD</b>                    |   |
|   | Cimetidine 400 mg twice/day   |
|   | Ranitidine/nizatidine 150 mg twice/day  |
|   | Famotidine 20 mg twice/day  |
|   | Therapy should be individualized to fit patient requirements; often effective when administered between breakfast and lunch, and between the evening meal and bedtime |
| <b>Erosive GERD</b>                       |   |
|   | Cimetidine 400 mg every 6 h   |
|   | Ranitidine/nizatidine 150 mg every 6 h  |
|   | Famotidine 40 mg every 12 h   |
| <b>PPIs</b>                               |   |
| <b>Nonerosive or erosive GERD</b>         |   |
|   | Omeprazole 20 mg daily or 20 mg twice/day   |
|   | Lansoprazole 30 mg daily or 30 mg twice/day   |
|   | Rabeprazole 20 mg daily or 20 mg twice/day  |
|   | Pantoprazole 40 mg daily or 40 mg twice/day   |
|   | All administered daily before breakfast; second dose, if necessary, should be given before evening meal   |

evening meal) should be attempted initially before substituting with another PPI. If symptoms persist, patients should undergo an endoscopic evaluation, and pH monitoring while on medication should be considered to confirm the presence of acid reflux and to assess the ability of the medications in effectively suppressing acid secretion. Peghini et al.<sup>115</sup> have advocated the use of H<sub>2</sub>-receptor antagonists at bedtime in such patients. This practice may be useful in some individuals, but caution must be exercised because of the undesirable effects of H<sub>2</sub>-antagonists on PPI activation discussed above. If the use of H<sub>2</sub>-blockers is being contemplated under such circumstances, it is preferable to use a short-acting agent to avoid any such interference. Truly refractory patients should be referred for consideration for antireflux surgery or experimental endoscopic forms of therapy.

Because GERD is a chronic disorder, maintenance therapy has also emerged as an important issue in the management of patients with the disease. Most patients with GERD, especially those with grade III and IV esophagitis, will relapse once therapy is discontinued.<sup>116</sup> In addition, maintenance of remission usually requires the same type and dose of medication that healed the initial esophagitis. A landmark study by Vigneri et al.<sup>117</sup> of maintenance therapy compared 5 regimens: ranitidine, cisapride, ranitidine plus cisapride, omeprazole, and omeprazole plus cisapride (Figure 7). All patients (n = 175) had esophagitis on initial endoscopy and were treated with 40 mg omeprazole daily for 8 weeks before starting one of the maintenance regimens (n = 35 for each group). After 12 months of treatment, remission was maintained in 80% of the omeprazole group vs. 54% in the cisapride and 49% in the ranitidine groups. Ranitidine plus cisapride was significantly better than ranitidine alone (66% remission), and the combination of

omeprazole plus cisapride was best of all, with an 89% remission rate; however, the latter combination was not significantly better than omeprazole alone (80%).<sup>117</sup> This study is representative of maintenance trials of GERD, showing significantly better remission rates with PPI therapy than with H<sub>2</sub>-antagonists or prokinetic regimens.

PPIs are also effective in the treatment of esophageal strictures, a well-known complication of erosive GERD. Management of strictures consists of endoscopic dilation and antisecretory therapy to heal esophagitis. Studies comparing PPI to H<sub>2</sub>-antagonist therapy have shown that the former heals esophagitis more effectively and decreases the eventual number of esophageal dilations required to relieve dysphagia.<sup>118,119</sup> Medical therapy in cases of Barrett's esophagus is aimed at healing the associated esophagitis. PPIs are effective in promoting healing, but do not appear to reduce the length of Barrett's segments. Interestingly, patients treated with PPIs in several studies did develop islands of squamous mucosa within the Barrett's segments.<sup>120</sup> However, to date, no studies have shown true regression of Barrett's esophagus or a decrease in the risk of esophageal malignancy with medical therapy. Similarly, antireflux surgery clearly heals esophagitis and relieves symptoms, but it does not produce regression of the Barrett's mucosa.<sup>121</sup>

The role of duodenogastric reflux of bile in the pathogenesis of GERD remains controversial. Vaezi and Richter<sup>122</sup> found that acid and duodenogastric bile reflux commonly occurs simultaneously in patients with complicated and severe GERD. However, they also reported that esophageal mucosal injury as a result of bile acids is pH dependent. PPIs not only decrease gastric volume, thereby decreasing gastroesophageal reflux, but also increase intraluminal pH, resulting in precipitation of conjugated bile acids. Zhang et al.<sup>123</sup> recently demonstrated that dihydroxy bile acids, such as deoxycholate and chenodeoxycholate, may induce cyclooxygenase 2 transcription in human esophageal carcinoma cells, an effect that may explain their tumor-promoting effects. Whether bile acids promote the progression of Barrett's metaplasia to dysplasia has not yet been determined.

A recent study by Lagergren et al.<sup>124</sup> reported a strong etiologic relationship between adenocarcinoma of the esophagus and GERD, with the greatest risks correlating with more frequent, more severe, and longer-lasting reflux. They also reported that patients treated medically had a greater cancer risk than those who were not. It is highly unlikely that medical therapy itself increases the risk of esophageal adenocarcinoma. Nevertheless, while antireflux therapy is clearly indicated for the management of GERD, no studies to date have proven that either

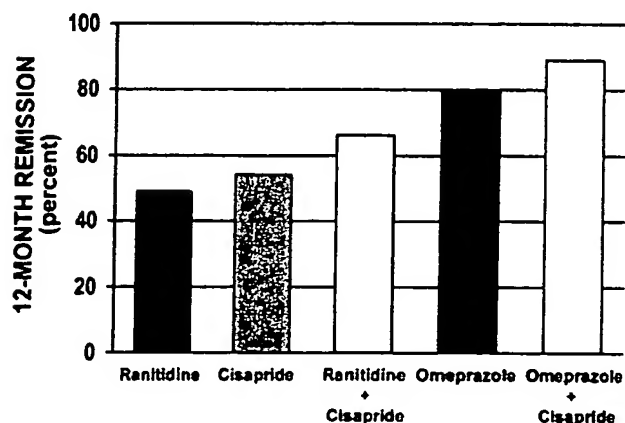


Figure 7. Comparison of 5 regimens used as maintenance therapy in patients with erosive GERD. Data represent the mean percentage of patients in remission after 12 months of therapy. Data from Vigneri et al.<sup>117</sup>



medical or surgical treatment alters the natural history of Barrett's esophagus. The results of these studies thus emphasize the need for continued surveillance of patients with Barrett's esophagus despite maximal acid suppression with PPIs or surgical therapy. Fundoplication offers the theoretical advantage of decreasing both gastroesophageal and duodenogastric reflux, but many endoscopists have found Barrett's surveillance technically far more difficult in surgically treated individuals.

It has become increasingly evident in recent years that a number of tracheopulmonary and other extraesophageal symptoms may occur as a result of acid reflux. In reflux-induced asthma, airway reactivity may be caused by either the aspiration of refluxed gastric contents or by vagally mediated bronchoconstriction induced by the presence of acid in the esophagus. Previous studies have indicated that 34%–89% of patients with asthma have concomitant GERD. However, because GERD and asthma are such common entities, an etiologic relationship has been difficult to establish. An uncontrolled trial of 30 patients with asthma and GERD proven by pH monitoring conducted by Harding et al.<sup>125</sup> showed that a 3-month course of omeprazole led to symptom improvement or improved pulmonary function in 73% of subjects. In this study, most of the improvement was detected in a small group of individuals, suggesting that acid reflux may be the principal asthma trigger in a small, but as yet undefined, group of individuals. Unfortunately, no randomized, controlled studies evaluating the efficacy of antisecretory therapy for asthma have been performed to date. Although idiopathic hoarseness and other symptoms of chronic laryngitis have been associated with GERD in several small series, studies evaluating the precise etiologic relationship between otolaryngologic symptoms and GERD are likewise lacking in rigor. Interestingly, in studies that included pH monitoring of patients with laryngeal symptoms and GERD, a significantly higher incidence of proximal acid reflux was detected in patients with otolaryngologic symptoms, suggesting that direct acid exposure probably contributes to the otolaryngologic symptoms in these patients.<sup>126</sup> Trials of therapy in these patients are either small or uncontrolled, but they do suggest true benefit in patients treated with PPIs generally administered in 2 doses (before breakfast and before the evening meal).<sup>127</sup>

Noncardiac chest pain (NCCP) refers to a syndrome of substernal chest pain in patients with no identifiable cardiac disease. Many individuals with this disorder appear to have an esophageal source for their symptoms, with GERD and esophageal dysmotility disorders accounting for the majority of cases in which an esophageal origin of the pain syndrome is identified. The history

alone does not satisfactorily distinguish between cardiac and esophageal etiologies of chest pain with sufficient accuracy, and classic anginal symptoms may occur with chest pain of esophageal origin. It is thus imperative to first exclude ischemic heart disease before embarking on a gastroenterological evaluation. Several studies, however, have shown that acid reflux is the most common cause of NCCP, accounting for 25%–50% of cases in several studies.<sup>128</sup> Once a cardiac etiology of chest pain has been excluded, an endoscopy is recommended to search for gastroduodenal ulcer, esophageal or gastric cancer, or esophagitis (infectious or reflux-related). If the endoscopy is unrevealing, nonerosive GERD may still be the etiology of chest pain, and an empirical trial of PPI therapy is recommended.<sup>129,130</sup> Fass et al.<sup>130</sup> recently demonstrated the usefulness of such an empirical trial in determining the etiologic significance of GERD in such individuals. If symptoms persist despite 12 weeks of therapy, ambulatory pH monitoring while the patient is on therapy may be useful in assessing the adequacy of acid suppression and documentation of reflux episodes. This evaluation is often done in conjunction with esophageal manometry to identify any esophageal dysmotility that may be responsible for NCCP.

In general, it appears reasonable to recommend that patients with extraesophageal symptoms possibly related to GERD be given at least a 2–3-month empirical trial of PPI therapy, with doses administered before breakfast and before the evening meal.<sup>129</sup> If symptoms do improve, it can be surmised that the symptoms are probably acid related. If symptoms persist, a 24-hour esophageal dual-probe pH study should be performed to determine whether acid suppression has been achieved. If patients remain symptomatic despite adequate acid suppression, it may be assumed that symptoms are not caused by acid reflux, provided that therapy has been optimal for a sufficient period.

Recently, an association between long-term PPI use and atrophic gastritis was postulated. In a study by Kuipers et al.<sup>131</sup> of patients with GERD treated either with antireflux surgery or omeprazole maintenance therapy, atrophic gastritis was detected after 5 years of treatment in 31% of PPI-treated patients who were *H. pylori* positive. During this same period, none of the patients treated surgically developed atrophic gastritis.<sup>131</sup> Eissele et al.<sup>132</sup> also reported that *H. pylori*-positive individuals treated with lansoprazole were at increased risk for the progression of fundic atrophy and the development of argyrophil cell hyperplasia. In this study,<sup>132</sup> no patient developed dysplastic changes or carcinoid tumor formation, and atrophic changes worsened primarily during the first 2 years of therapy, with

little deterioration thereafter. Such observations led to concern over the possibility that long-term PPI therapy in *H. pylori*-infected patients might lead to an increased incidence of atrophic gastritis and possibly adenocarcinoma, and some recommendations were thus made to eradicate the organism in all patients before initiating extended courses of PPI therapy. However, similar studies in the United States and Scandinavia have not confirmed this increase in atrophic gastritis with PPI use, and an FDA summary based on available data determined that atrophic gastritis was not a significant complication of PPI therapy in *H. pylori*-infected patients.<sup>133,134</sup> In addition, no studies have actually reported the development of dysplasia or gastric adenocarcinoma in humans, which generally occurs only after decades of atrophic gastritis and achlorhydria. Furthermore, recent studies have suggested that the antisecretory properties of PPIs may be enhanced in the setting of *H. pylori* infection<sup>135</sup> and that *cagA*-positive strains of *H. pylori* may actually protect individuals against the development of esophageal adenocarcinoma.<sup>136</sup> Finally, el-Serag and Sonnenberg<sup>137</sup> recently reported that, although a cause-and-effect relationship has not been clearly established, the incidence of *H. pylori* infection and ulcer disease appears to be inversely proportional to the incidence of GERD. Therefore, presently, routine eradication of *H. pylori* infection does not appear warranted in individuals with GERD in whom long-term PPI therapy is being contemplated. Long-term studies will be necessary to determine whether certain groups of individuals might benefit from antimicrobial treatment.

**Antisecretory medication in the treatment of GERD.** The question of which antisecretory drug regimen is optimal for the treatment of GERD has been the subject of ongoing debate. Advocates for both "step-down" (starting with a PPI and then converting a patient to long-term H<sub>2</sub>-antagonist therapy) and "step-up" therapy present compelling arguments. With the availability of inexpensive generic H<sub>2</sub>-antagonists, many physicians and particularly managed-care organizations have opted for the latter approach exclusively, and in doing so have often unnecessarily delayed effective therapy with PPIs, which at present are more costly. It is imperative that the overall direct costs of treating any disorder be considered, rather than merely the price of each individual tablet or capsule. The development of complications and long-term sequelae,<sup>124</sup> as well as patient satisfaction and work days lost, both of which contribute to the indirect costs associated with treating GERD, should be part of the equation in developing strategies for choosing antisecretory class. Complete symptom relief and mucosal healing should be the goal in all individuals with GERD.

Despite the unequivocal superiority of PPIs over H<sub>2</sub>-receptor antagonists in both relieving symptoms and in healing esophagitis, the majority of individuals with acid reflux disease have mild-to-moderate, intermittent symptoms, usually in the absence of esophageal mucosal injury. Therefore, in many individuals, initial treatment with H<sub>2</sub>-receptor antagonists may be effective in providing symptom relief. Another argument in favor of a "step-up" approach is the property of PPIs to produce rebound acid hypersecretion,<sup>138</sup> particularly in individuals not infected with *H. pylori*, a phenomenon that may render H<sub>2</sub>-antagonists ineffective and mandate the continued use of a PPI. Also, as discussed previously, PPIs are not effective inhibitors of gastric acid secretion when given only "as needed," and it is difficult to advocate continuous treatment with a PPI under such circumstances, unless it is the only regimen that provides satisfactory symptomatic improvement. In general, the treatment of GERD differs significantly from the treatment of gastroduodenal ulcer, in which "one dose (of medication) fits all." Specific recommendations for the use of antisecretory medication in treating GERD vary significantly among individuals and clearly are dependent on the frequency and severity of the symptoms and the presence or absence of mucosal injury. Furthermore, in contrast to ulcer disease, in which maintenance therapy can usually be accomplished using a dose of medication lower than the one necessary for healing an active ulcer, the drug regimen used to initially heal esophagitis and control GERD symptoms is commonly the same one required to maintain an individual in remission. The final decision is one that each physician must make, often with input from individual patients. Figure 8 offers a suggested approach to the use of antisecretory medication in the treatment of GERD.

### Stress-Related Erosive Syndrome

The treatment of established or presumed SRES involves the institution of nonpharmacologic medical principles applicable to the care of the critically ill patient at risk, including adequate and aggressive volume resuscitation,<sup>139-141</sup> antimicrobial therapy (especially for intra-abdominal sources of sepsis),<sup>142</sup> and optimal tissue oxygenation.<sup>143</sup> In addition, because luminal acid plays a dominant role in producing the multiple erosive lesions characteristic of the entity, alkalization of the gastric lumen has historically comprised the mainstay form of prophylactic therapy in preventing GI hemorrhage associated with this entity.

**Antacids.** Several placebo-controlled trials have demonstrated the efficacy of antacids in significantly reducing the frequency of overt and clinically significant



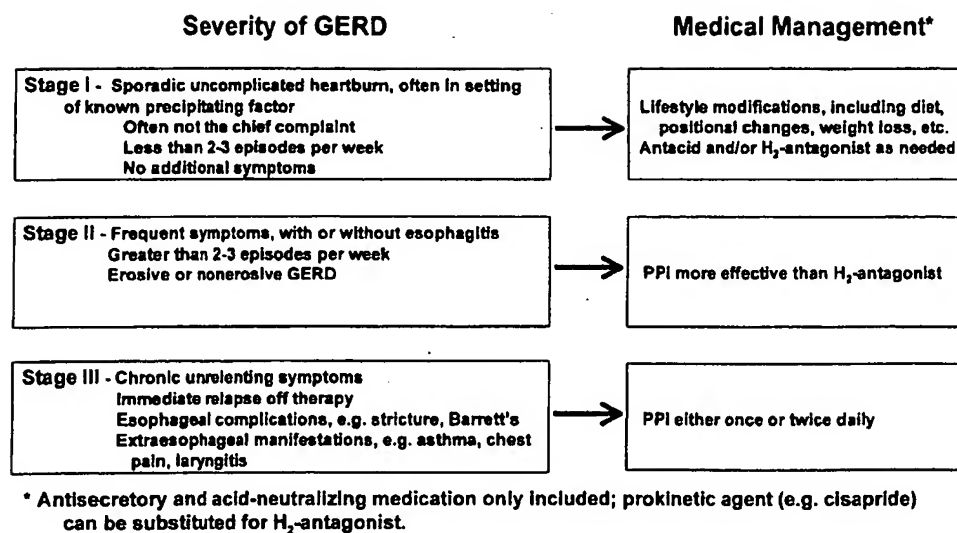


Figure 8. A suggested approach to the use of acid-neutralizing and antisecretory medication in the treatment of GERD of different severity.

GI bleeding from SRES.<sup>144,145</sup> Antacids exert their beneficial effects by decreasing intragastric acidity through direct neutralization and by binding pepsin,<sup>145</sup> although other studies have postulated additional gastroprotective mechanisms.<sup>146,147</sup> Aluminum-based compounds appear to increase mucus and bicarbonate production, increase gastric mucosal blood flow, bind potentially injurious agents like bile acids, and stimulate epithelial cell renewal.<sup>145</sup> The goal of acid neutralization is to increase the intragastric pH to 4 or greater to prevent the catalytic conversion of pepsinogen to its biologically active form, pepsin, and thereby reduce proteolytic activity in the gastric lumen. In addition, platelet aggregation normalizes above a pH of 5.9, which provides further protection against hemorrhage. Antacids are typically administered as 30–60-mL aliquots orally or via a nasogastric tube every 1–2 hours.<sup>148,149</sup> The regimen requires close monitoring of intragastric pH and individual titration to maintain the intragastric pH above 4. In addition to diarrhea, which can be quite severe because of the volume of antacids needed to maintain the luminal pH above 4, the side effects of magnesium-containing antacids include alkalemia and hypermagnesemia, and aluminum-based antacids cause hypophosphatemia, constipation, and metabolic alkalosis, as well as potentially toxic plasma aluminum levels in patients with renal insufficiency.<sup>150</sup> Furthermore, all antacids can impair the systemic absorption of drugs, including antibiotics and H<sub>2</sub>-antagonists.<sup>151</sup>

**Histamine H<sub>2</sub>-receptor antagonists.** H<sub>2</sub>-receptor antagonists have been shown unequivocally to reduce the incidence of overt and clinically significant SRES-associated hemorrhage when compared with untreated controls.<sup>145,152</sup> A meta-analysis of 16 studies involving 2133 patients by Shuman et al.<sup>153</sup> showed no significant

difference in efficacy between antacids and H<sub>2</sub>-receptor antagonists in preventing clinically significant hemorrhage caused by SRES. Moreover, both regimens were shown to be superior to placebo and were tolerated equally well. More recently, a meta-analysis by Tryba et al.<sup>145</sup> has suggested that H<sub>2</sub>-blockers may be more effective than antacids in SRES prophylaxis. Cimetidine is typically administered intravenously by continuous infusion at doses of 37.5–100 mg/h, while ranitidine is dosed at 6.25–12.5 mg/h and famotidine at 1.7–2.1 mg/h. All can be administered with or without a loading dose,<sup>37</sup> although as discussed above, dose adjustments are necessary for individuals with impaired renal function (Table 2). Continuous H<sub>2</sub>-receptor antagonist infusion appears to provide more stable acid suppression than intermittent administration.<sup>37,154–157</sup> Currently, because of their efficacy and excellent safety profile, as well as ease of administration, H<sub>2</sub>-receptor antagonists are generally preferred over antacids and PPIs in the prevention of SRES-associated GI hemorrhage. A potential problem with their use, however, might arise once a patient resumes feeding and a decision is made to continue antisecretory therapy, but to change to an oral PPI. Studies to examine this question have yet to be performed, but a reasonable suggestion would be to wait a period of 6–8 hours between stopping parenteral cimetidine and ranitidine and 10–12 hours after discontinuing famotidine before starting feeding and initiating therapy with a PPI.

**PPIs.** Some controversy exists regarding the role of PPIs in SRES prophylaxis. Despite a few small studies suggesting a beneficial effect,<sup>158,159</sup> no large randomized, clinical trials have been performed to date to reliably assess the true benefit of these agents in preventing SRES-associated GI hemorrhage. Two recent studies in

mechanically ventilated ICU patients suggested that a simplified omeprazole suspension may not only prevent clinically significant SRES-induced hemorrhage but also is safe and cost-effective.<sup>160,161</sup> However, the study designs were limited in scope, and patient numbers were small. Furthermore, omeprazole and other PPIs have an enteric coating that has been formulated to dissolve at an alkaline pH. The instillation of these granules through a nasogastric tube might disrupt this coating within the gastric lumen, which may cause acid-catalyzed conversion to its reactive species. Finally, it must be emphasized once again that PPIs are prodrugs, which are normally activated after systemic absorption in the highly acidic milieu of the secretory canaliculus of *activated* parietal cells.<sup>162,163</sup> Activation occurs after a meal, and because individuals at risk for the development of SRES are generally fasting, these drugs would be significantly less active.<sup>162</sup> Despite a prolonged biological half-life, the plasma half-life of PPIs is quite short (2–3 hours), and if administered intermittently, several doses would be required to achieve adequate inhibition of  $H^+, K^+$ -ATPase. The initial dose of the PPI will only inhibit activated  $H^+, K^+$ -ATPase present in the canalicular membrane, and as inactive enzyme is continuously recruited into the secretory canaliculus, acid secretion will resume after a short period of inhibition. Only pantoprazole is currently available in the United States as an intravenous preparation,<sup>163</sup> and although no studies examining this agent in the prophylaxis of SRES have been reported, the continuous infusion of this agent might be expected not only to adequately inhibit acid secretion, but also to allow a smooth transition to oral PPI therapy. Until these issues are resolved with the performance of well-designed, randomized, controlled trials, it seems that  $H_2$ -receptor antagonists are preferred over the PPIs in preventing GI hemorrhage associated with SRES.

**Inhibition of acid secretion and nosocomial pneumonia.** The possibility of an increased risk of nosocomial pneumonia has been suggested as a complication of antisecretory therapy for SRES. This notion stemmed from studies showing that gastric bacterial colonization can occur after only a few days of an alkaline intragastric milieu (pH > 4). In addition, a higher gastric pH correlates directly with logarithmic increases in the concentration of gram-negative organisms in the gastric aspirate.<sup>164</sup> In a large study of mechanically ventilated patients at risk for the development of SRES, Driks et al.<sup>165</sup> reported a pneumonia rate of 12% with sucralfate, a basic nonabsorbable aluminum salt of sucrose octasulfate, compared with a 23% incidence in the group receiving antisecretory medication consisting of cimetidine with or without antacids. Upon stratification,

antacids were associated with a 23% incidence of pneumonia, while only 5.9% of the  $H_2$ -receptor antagonist group (lower than those receiving sucralfate) developed pneumonia, implicating antacids, and not  $H_2$ -blockers, as the culprit. Antacids increase gastric volume and thereby might increase the potential for aspiration, while the gastric volume of patients on antisecretory agents is clearly diminished.<sup>165</sup> A more recent meta-analysis of trials by Cook et al.<sup>166</sup> examined drug class-specific rates of nosocomial pneumonia and concluded that sucralfate causes significantly less pneumonia than  $H_2$ -antagonists. Unfortunately, in some studies, sucralfate was somewhat less effective than alkalinizing agents in preventing SRES-associated GI hemorrhage.<sup>165,167–170</sup>

Taking all these issues into consideration, it would appear that the positive attributes of  $H_2$ -receptor antagonists outweigh the risk of nosocomial pneumonia associated with their use. Their intravenous administration obviates the need for a nasogastric tube, which is often necessary when administering antacids or a sucralfate "slurry," and not only causes discomfort, but also may serve as a conduit for the migration of bacteria from the stomach to the pharynx.<sup>165</sup> Although the use of a PPI, like pantoprazole, by primed continuous infusion offers a theoretical advantage in the transition from intravenous to oral therapy, any recommendation regarding their use in preventing GI hemorrhage associated with SRES must await formal trials evaluating their efficacy and safety.

### GI Hemorrhage

Although a few reports have suggested benefit associated with the use of antisecretory agents in the control of nonvariceal GI hemorrhage,<sup>171,172</sup> most have found these agents to be ineffective.<sup>173,174</sup> The rationale for the use of antisecretory agents stems from the notion that at least two-thirds of cases of GI bleeding are associated with an acid-related disorder, such as gastroduodenal ulcer, gastritis, and esophagitis. In addition, after initial clot formation, the avoidance of clot lysis may reduce recurrent hemorrhage. Previous studies have shown that both clot formation and the prevention of clot lysis occur more effectively at higher pH levels.<sup>175,176</sup> The only antisecretory agents that have been examined to any extent are the  $H_2$ -receptor antagonists and PPIs. Somatostatin also inhibits acid secretion by several mechanisms, and although this regulatory peptide and its analogues have been evaluated in the treatment of both variceal and nonvariceal GI hemorrhage, its principal effect appears to be a reduction in splanchnic/portal blood flow.

**$H_2$ -receptor antagonists.** No single study has convincingly demonstrated an overall benefit of  $H_2$ -antagonists in the cessation of acute upper GI hemor-

rhage or in the prevention of recurrent bleeding. However, Collins and Langman<sup>171</sup> reported a meta-analysis of 27 randomized, controlled trials involving more than over 2500 individuals with upper GI bleeding who had been treated with H<sub>2</sub>-antagonists. The odds ratio for a beneficial effect of H<sub>2</sub>-blockers on the cessation of bleeding, the need for surgical intervention, and mortality were 0.89 ( $P = \text{NS}$ ), 0.78 ( $P = 0.05$ ), and 0.70 ( $P = 0.02$ ), respectively. The authors of this study concluded that therapy with H<sub>2</sub>-antagonists "... appears to be moderately promising, but... still needs to be assessed reliably. To detect... effect reliably might require randomization of 10,000 patients or more."<sup>171</sup>

**PPIs.** The recent availability of more potent inhibitors of gastric acid secretion has renewed interest in the use of such agents in controlling upper GI hemorrhage. In a double-blind, placebo-controlled trial, Daneshmend et al.<sup>177</sup> examined the effects of omeprazole in 1147 patients with nonvariceal upper GI hemorrhage. Omeprazole was given intravenously on the first day, followed by 80 mg daily for the next 72 hours. No significant differences were detected between the omeprazole and placebo groups with regard to control of hemorrhage, transfusion requirements, or the need for surgical intervention. In a second study by Khuroo et al.,<sup>172</sup> 220 patients with bleeding duodenal, gastric, or stomal ulcers were randomized to 40 mg omeprazole or placebo orally every 12 hours for 5 days. Bleeding continued in 10.9% and 36.4% of the patients receiving omeprazole and placebo, respectively, and 29.1% and 70.9% of those receiving omeprazole and placebo, respectively, required blood transfusions (both  $P < 0.001$ ). While mortality was not reduced significantly in the omeprazole group, a trend favoring the PPI was observed (1.8% vs. 5.5%). It is important to note that endoscopic therapy, usually the modality of choice for bleeding ulcers, was not employed at all during the course of this trial.<sup>172</sup> Furthermore, despite benefit in this study, PPIs are activated after systemic absorption, which occurs following a meal, and because individuals with actively bleeding ulcers are usually fasting, these drugs would be significantly less active unless used frequently at higher doses or by continuous intravenous infusion.

More recently, Lin et al.<sup>178</sup> compared the effects of cimetidine and omeprazole, both administered by primed continuous intravenous infusion, in 100 patients with bleeding ulcers controlled initially by endoscopy, a contemporary approach more analogous to the current therapy of this clinical scenario in the United States. They found that omeprazole (160 mg/day) was more effective than cimetidine (1200 mg/day) in maintaining the intragastric pH above 6.0 and in preventing recurrent

ulcer-related hemorrhage (4% vs. 24%,  $P = 0.004$ ). Therefore, because of the safety of antisecretory agents and the frequency of acid-related GI bleeding lesions, it is not unreasonable to treat individuals with hemorrhage from an upper GI source initially with either an H<sub>2</sub>-receptor antagonist or a PPI, preferably administered via the intravenous route, until diagnostic and therapeutic endoscopy can be performed. If an ulcer is detected at endoscopy, antisecretory drugs should be instituted after injection, thermal coagulation, or electrocoagulation to treat the active ulcer and possibly to prevent rebleeding.<sup>178,179</sup>

### Nonulcer Dyspepsia

An exhaustive review of an approach to the patient with nonulcer dyspepsia is beyond the scope of this manuscript and has been the subject of a recent review and position statement in *Gastroenterology*.<sup>180,181</sup> Moreover, the role of *H. pylori* infection in the etiology of dyspepsia, if any,<sup>182,183</sup> is discussed elsewhere in this Supplement. In general, patients with GERD and those with a biliary etiology, most of whom can be identified by obtaining a careful history, should ideally be removed from the category of nonulcer dyspepsia. Individuals with dyspeptic symptoms who fit specific criteria, which include age  $<45$  and the absence of any alarm symptoms, may be treated empirically with either antisecretory agents or prokinetic medication. The latter should be used if features suggestive of a motility disturbance are evident, such as concomitant features of irritable bowel syndrome, abdominal distention, eructations, or detection of a psychological disturbance. In most other settings, including dyspepsia associated with the use of NSAIDs,<sup>16</sup> antisecretory medications are often used and have been reported in some studies to be helpful in relieving symptoms.<sup>180,181,184</sup> However, with the exception of NSAID-related dyspepsia,<sup>16</sup> universal and unequivocal benefit of antisecretory agents in the symptomatic treat-

**Table 6.** Recommendations for Antisecretory Drug Treatment of Nonulcer Dyspepsia

|   |                  |
|---|------------------|
| <b>H<sub>2</sub>-receptor antagonists</b>   |                  |
| Cimetidine  | 400 mg twice/day |
| Ranitidine/nizatidine   | 150 mg twice/day |
| Famotidine  | 20 mg twice/day  |
| Therapy should be individualized to fit patient requirements; often effective when administered between breakfast and lunch, and between the evening meal and bedtime |                  |
| <b>PPIs</b>   |                  |
| Omeprazole  | 20 mg daily      |
| Lansoprazole  | 30 mg daily      |
| Rabeprazole   | 20 mg daily      |
| Pantoprazole  | 40 mg daily      |
| All administered daily before breakfast; second dose, if necessary, should be given before evening meal   |                  |

ment of dyspepsia has not been demonstrated.<sup>185,186</sup> Moreover, it is important to avoid introducing long-term drug use in individuals with "functional dyspepsia," particularly because of the considerable benefit of placebo in such individuals.<sup>186</sup> When employed, the initial doses of medication, whether H<sub>2</sub>-antagonist or PPI, should generally be low (Table 6), and dosing should be flexible and optimized to meet the individual needs of each individual. If used on an "on-demand" basis, H<sub>2</sub>-blockers offer an advantage over PPIs because of their relatively fast onset of action and, as discussed previously, the length of time necessary to achieve steady-state concentrations when using the latter.

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Address requests for reprints to: M. Michael Wolfe, M.D., Section of Gastroenterology, Boston Medical Center, 88 East Newton Street, Boston, Massachusetts 02118-2393. e-mail: michael.wolfe@bmc.org; fax: (617) 638-7785.

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*Sleisenger & Fordtran's*

# Gastrointestinal and Liver Disease

*Pathophysiology / Diagnosis / Management*

6th Edition

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Mark Feldman, M.D.  
Southland Professor and Vice Chairman  
Department of Internal Medicine  
University of Texas Southwestern  
Medical Center at Dallas  
Chief, Medical Service  
Department of Veterans Affairs Medical  
Center  
Dallas, Texas

Bruce F. Scharschmidt, M.D.  
Professor of Medicine  
Division of Gastroenterology  
University of California, San Francisco  
San Francisco, California  
Vice President, Clinical Affairs  
Chiron Corporation  
Emeryville, California

Marvin H. Sleisenger, M.D.  
Professor of Medicine  
University of California, San Francisco  
Distinguished Physician  
Department of Veterans Affairs  
Medical Center  
San Francisco VA Medical Center  
San Francisco, California

Nutrition Section Editor:  
Samuel Klein, M.D.  
Professor of Medicine  
Director, Center for Human Nutrition  
Washington University School of Medicine  
St. Louis, Missouri

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# Peptic Ulcer and Its Complications

• Andrew H. Soll

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Table 40.5 • Adverse Effects from Antiulcer Therapy

|                           | H <sub>2</sub> BLOCKERS   | OMEPRAZOLE | SUCRALFATE | ANTACIDS   |
|---------------------------|---|------------|------------|--|
| Toxic effects             | Hypochlorhydria;<br>Bacterial overgrowth;<br>Hypergastrinemia;<br>Altered absorption from alkalinization;<br>Decreased absorption of divalent cations;<br>Decreased vitamin B <sub>12</sub> absorption  |            |            |  |
| Side effects              | Antiandrogenic; cimetidine central nervous system reactions;<br>headaches; immune modulation;<br>cardiac conduction abnormalities;<br>idiosyncratic hepatic injury;<br>immune hypersensitivity reactions; thrombocytopenia;<br>granulocytopenia |            |            | Aluminum absorption;<br>phosphate depletion  |
| Drug interactions         |   |            |            |  |
| Absorption                | Intraluminal alkalinization, inhibits absorption (e.g., ketoconazole)   |            |            | Intraluminal drug binding of tetracycline, ciprofloxacin, isoniazid, chloroquine, warfarin, digoxin, phenytoin, quinidine, aspirin and other nonsteroidal anti-inflammatory drugs, cimetidine, ranitidine, ferrous sulfate, theophylline |
| P <sub>450</sub> mediated | Cimetidine (>ranitidine)<br>Warfarin, theophylline, phenytoin, diazepam, propranolol  |            |            | Diazepam, warfarin, phenytoin  |
| Excretion                 | ↓ Renal tubular excretion of proguanide   |            |            |  |

tion); (2) side effects, which reflect actions unrelated to the primary therapeutic action; and (3) drug interactions.

H<sub>2</sub>RAs are remarkably safe drugs: in randomized trials, adverse reactions are similar to placebo.<sup>241</sup> However, a number of uncommon side effects have been reported, primarily as isolated cases or in retrospective, uncontrolled series. However, causality cannot be established from the temporal association between drug use and an untoward effect, particularly when the clinical situation is complicated by serious medical illness and the use of multiple drugs.<sup>242</sup> In addition, solid conclusions regarding causality can only be drawn with drug rechallenge, which is rarely performed. Although differences exist among H<sub>2</sub>RAs, the focus has been on cimetidine for several reasons: (1) the reporting of side effects is directly proportional to the clinical experience with a compound; (2) side effects are more commonly reported when the class of compounds is newly introduced; and (3) bias is created once a drug is linked to a putative side effect.<sup>243</sup> Therefore, in the absence of controlled comparisons, only limited conclusions can be drawn regarding the relative occurrence of uncommon side effects with the H<sub>2</sub>RAs.

Cimetidine produces gynecomastia and impotence in dose- and time-dependent fashion. Gynecomastia is rare with less than 8-week treatment at normal doses and occurred in only 0.2% of men treated for 26 weeks.<sup>244</sup> Gynecomastia and impotence occurred in half of the males with hypersecretory disorders taking prolonged, high-dose cimetidine therapy; gynecomastia and impotence gradually resolved when ranitidine replaced cimetidine.<sup>245</sup> Rare reports with other H<sub>2</sub>RAs suggest that this effect is specific for cimetidine.

Several mechanisms can potentially mediate the immune and hematopoietic effects of H<sub>2</sub>RAs: (1) idiosyncratic reactions of the immune hypersensitivity type; (2) idiosyncratic

reactions occurring by unknown mechanism; (3) effects mediated by blockade of pharmacologically typical H<sub>2</sub> receptors; or (4) pharmacologic effects independent of the H<sub>2</sub> receptor. H<sub>2</sub> receptors are present on suppressor T lymphocytes, and blockade of these receptors appears to enhance cell-mediated immunity.<sup>246, 247</sup> Concern persists that occasionally H<sub>2</sub>RAs may enhance transplant rejection and autoimmune or allergic disease processes. Most studies have been done with cimetidine; some immunomodulatory effects may reflect a unique action of the imidazole ring of cimetidine rather than actions at H<sub>2</sub> receptors. Comparative data with other H<sub>2</sub>RAs are limited and conflicting.<sup>247</sup> Other uncommon reactions may be mediated by immune mechanisms, including polymyositis and interstitial nephritis with cimetidine.<sup>242, 247</sup> An immune-complex rash has been reported with ranitidine. Fever has been associated with both cimetidine and ranitidine.<sup>248</sup>

H<sub>2</sub>RAs have been implicated in rare, idiosyncratic cases of myelosuppression, thrombocytopenia, neutropenia, anemia, and pancytopenia.<sup>248</sup> They have also been implicated in hemolytic anemia, although no antidrug antibodies or hemolysis on rechallenge was found.<sup>249</sup> Thrombocytopenia has also been linked to hypersensitivity to ranitidine.<sup>242</sup> In about 5% of patients undergoing bone marrow transplantation, ranitidine was implicated as the possible cause of myelosuppression.<sup>249</sup>

CNS symptoms, including confusion, restlessness, somnolence, agitation, headaches, and dizziness, have been reported with H<sub>2</sub>RAs. Hallucinations, focal twitching, seizures, unresponsiveness, and apnea have been implicated if therapy is continued.<sup>242, 243</sup> CNS side effects from any H<sub>2</sub>RAs are rare during outpatient therapy. Mental status changes have been reported particularly in elderly patients in an ICU with renal or hepatic dysfunction,<sup>243</sup> although the incidence of such symptoms with H<sub>2</sub>RAs varies greatly among studies. Age and

multiple system failure predispose to CNS symptoms in the ICU setting, with this background preventing firm conclusions regarding the risk of CNS side effects from H<sub>2</sub>RAs.<sup>241</sup> There have been limited rechallenges with the H<sub>2</sub>RAs, which supports a causal effect.<sup>242</sup> However, proving exacerbation of "TCU-itis" by a single drug would require large, randomized controlled trials,<sup>243</sup> which have not been performed. Cimetidine has been implicated as the most frequent cause of these CNS symptoms, but CNS side effects have also been reported with ranitidine and famotidine.<sup>242, 243</sup> Ranitidine also has been reported to produce headaches, with positive rechallenge in a few cases.<sup>243, 249</sup> Because of the inadequacy of the literature and the biases noted earlier, the relative impact of the different H<sub>2</sub>RAs remains uncertain. Whether these side effects occur less frequently with continuous intravenous dosage remains to be established. These CNS effects are reversible on discontinuation of drug.

Transient, small increases in liver enzyme levels, particularly those of serum transaminases, can occur with H<sub>2</sub>RAs, especially with high intravenous doses, but these changes resolve during continued therapy. None of the four H<sub>2</sub>RAs are hepatotoxic, but rare, idiosyncratic, or apparent immune hypersensitivity hepatitis, with rash, fever, or eosinophilia has been reported.<sup>239, 251</sup> Generally the acute hepatitis is rapidly reversible after withdrawal of the agent; rechallenge has been positive in a few cases. Because these events are rare and the causality uncertain, serial monitoring of liver chemistries is not justified. However, it is prudent to check hepatic enzyme levels about 5 days into high-dose intravenous therapy. If hepatitis develops in a patient on H<sub>2</sub>RAs, the drug should be immediately discontinued. If continuation of H<sub>2</sub>RAs therapy is required, after resolution of the liver chemical abnormalities, one of the other H<sub>2</sub>RAs should be used and liver chemistry carefully monitored.

Cardiac effects, such as sinus bradycardia, hypotension, atrioventricular block, prolongation of the QT interval, and sinus and cardiac arrest have occurred with the rapid infusion of H<sub>2</sub>RAs, although oral therapy has been also incriminated in producing cardiac effects.<sup>238, 252</sup> H<sub>2</sub> receptors are present in the heart, and H<sub>2</sub>RAs reduce heart rate and cardiac output during submaximal exercise or after sufficient oral doses (i.e., nizatidine, 300 or 600 mg).<sup>252</sup> With the existence of cardiac H<sub>2</sub> receptors, caution is appropriate with these antagonists, although clinically significant effects on sinus rhythm or conduction are rare. Possible risk factors for cardiac effects include rapid IV infusion, high dose, conditions that would delay drug clearance (e.g., renal or hepatic dysfunction), and underlying cardiac disease.<sup>238</sup>

## Proton Pump Inhibitors

**Mechanism of Action.** See Chapter 38.

**Formulation and Absorption.** The PPIs (omeprazole, lansoprazole, and pantoprazole) are prodrugs that are acid labile and inactivated if permitted to dissolve in acidic gastric juice. Therefore, enteric-coated granules are used for the oral preparations; these granules only dissolve when encountering a pH above 6. After a buffered suspension, omeprazole is rapidly absorbed and peak plasma levels are reached in 30 minutes; the half-life in the serum is 1 hour.<sup>253</sup> Absorption from the

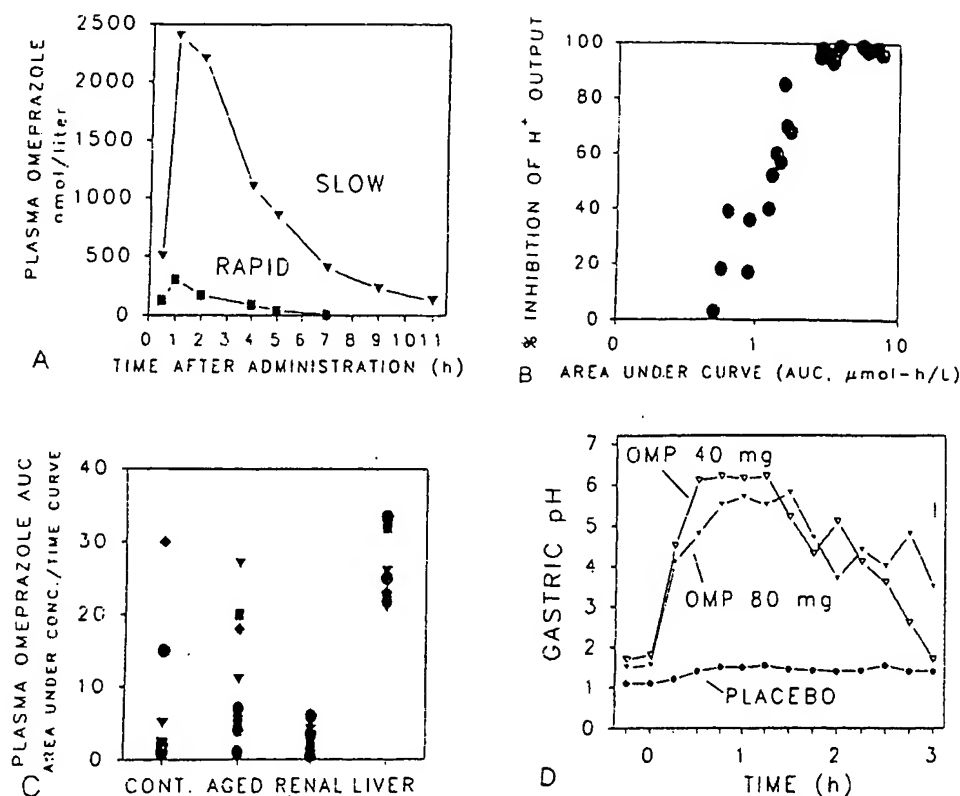
enteric-coated granules is slower, with peak concentrations occurring 1 to 3 hours after dosing and the drug detectable in serum for about 6 hours (Fig. 40-15A).<sup>253</sup> The effectiveness of a PPI when given by oral administration relates closely to the area under the plasma concentration-time curve (AUC), rather than to peak plasma drug levels (see Fig. 40-15B).<sup>253, 257</sup> The prolonged duration of PPI antisecretory action reflects irreversible inactivation of the parietal cell H<sup>+</sup>K<sup>+</sup>-ATPase, rather than a prolonged serum half-life. Administering omeprazole with food delays absorption but does not alter the AUC.<sup>258, 262</sup> In contrast, the bioavailability of lansoprazole in single-dose studies appears to be reduced by administration with food, but available data suggest that consequences for antisecretory efficacy are minimal.<sup>256</sup> In general, the pharmacokinetics for the three PPIs are similar.

**Hepatic Metabolism and Excretion.** Omeprazole and lansoprazole are metabolized in the liver by the CYP3A4 and CYP2C members of the cytochrome P-450 (CYP) superfamily.<sup>256, 258-260</sup> The CYP2C isoforms involved in metabolizing the PPI include CYP2C18 or 19 (see later) and probably 2C8.<sup>257, 259, 261, 262</sup> The metabolites are inactive and are excreted mostly in urine; PPI clearance is not altered in renal failure.<sup>253, 256</sup> Pantoprazole is also metabolized by these two CYP families, although some metabolism occurs by phase II conjugation reactions.<sup>257</sup>

PPI clearance is significantly delayed with impaired hepatic function (see Fig. 40-15C).<sup>253, 258</sup> In elderly subjects the AUC varies, probably reflecting variation in clearance (see Fig. 40-15C).<sup>253</sup> Similar observations have been reported with lansoprazole.<sup>256</sup> In light of the wide safety margin with these drugs and the apparent absence of accumulation, there are few reasons to adjust the dose. However, it is appropriate to decrease the PPI dose in the presence of hepatic failure.

In a few percent of normal subjects, hepatic metabolism of omeprazole is delayed (see Fig. 40-15A), with the AUC increased about 10-fold.<sup>263</sup> This abnormality probably reflects inherited variation in activity of the CYP2C19 isoform that also metabolizes S-mephenytoin.<sup>260</sup> Drug accumulation does not occur in slow metabolizers with a daily dosing schedule because the drug is cleared in this period. However, acid-secreting inhibition should be more prominent in slow metabolizers; indirect evidence supporting this point is the finding of somewhat higher gastrin levels in slow metabolizers with 7 days of PPI therapy, compared with normal subjects.<sup>260</sup> This abnormality of CYP2C19 occurs in about 3% of whites, about 5% of blacks, and about 15% of Asians.<sup>260</sup> Lansoprazole appears to be metabolized by the distinct CYP2C18 isoform.<sup>256</sup> Although considerable variation in the AUC for lansoprazole occurs among individuals,<sup>256, 262</sup> the existence of distinct "slow metabolizers" is uncertain.<sup>256</sup>

**Adverse Effects.** Omeprazole and lansoprazole have very few side effects,<sup>256, 265</sup> although clinical experience with omeprazole is much more extensive than lansoprazole (see Table 40-5). Their excellent safety profile may reflect the fact that the PPI prodrugs are selectively activated in the acidic compartment of the parietal cell. However, caution is appropriate regarding rare or delayed untoward effects, especially with newer agents. The largely theoretical consequences relating to prolonged acid inhibition, hypergastrinemia, and hyperplasia of enterochromaffin-like (ECL) cells are considered elsewhere (see Chapter 38). Leydig cell tumors have been reported in



**Figure 40-15.** Omeprazole pharmacokinetics and pharmacodynamics. **A.** The plasma concentration curve for rapid and slow metabolizers is shown as a function of time after a 20-mg dose of omeprazole. (Data from Andersson, T., Cederberg, C., Edvardsson, G., et al. Effect of omeprazole treatment on diazepam plasma levels in slow versus normal rapid metabolizers of omeprazole. *Clin. Pharmacol. Ther.* 47:79, 1990.) **B.** The inhibition of acid secretion by omeprazole is shown as a function of the area under the plasma concentration curve (AUC). (Data from Lind, T., Cederberg, C., Ekenved, G., et al. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin stimulated acid secretion in man. *Gut* 24:270, 1983.) **C.** The AUC after omeprazole administration is illustrated for control and elderly subjects and patients with renal and liver failure. (Data from Cederberg, C., Andersson, T., and Skaanberg, I. Omeprazole: Pharmacokinetics and metabolism in man. *Scand. J. Gastroenterol.* 24(Suppl 166):33, 1989.) **D.** Time course for gastric pH after intravenous administration of 40 or 80 mg of omeprazole to fasting subjects. (Data from Baak, L. C., Jansen, J. B. M. J., and Lamers, C. B. H. W. Effect of intravenous omeprazole on intragastric pH during intravenous infusion of amino acids. *Dig. Dis. Sci.* 35:596, 1990.)

rats treated with lansoprazole: the mechanism appears to be suppression of testosterone synthesis by a lansoprazole metabolite.<sup>266</sup> Luteinizing hormone (LH) secretion is enhanced owing to decreased testosterone feedback, and both the LH increase and tumor formation are suppressed by testosterone replacement therapy.<sup>266</sup> Apparently, there is considerable species variability in the formation of the metabolites that inhibits testosterone synthesis: in humans, this metabolite has not been detected and no effects on testosterone synthesis or LH release have been reported. However, long-term monitoring of a larger group of subjects is needed before relevance to human use can be firmly excluded. One concern is that cotherapy with other drugs that interact with cytochrome P450 may influence PPI metabolism or drug interactions.

**Clinical Inhibition of Acid Secretion.** The dose and time dependency of inhibition of acid secretion by PPIs have several features of clinical relevance:

1. A time lag of about 4 days occurs before peak antisecretory effectiveness is achieved for PPI, probably re-

flecting progressive inhibition of the  $H^+K^+$ -ATPase and possibly increases in drug bioavailability. This lag period is inversely related to dose. Although less data are available, the pattern appears similar with the other PPIs, lansoprazole and pantoprazole.

2. **Variability in antisecretory effectiveness** is evident for PPIs, probably due to variability in absorption and clearance as reflected in the AUC. After 7 days of therapy on the 10-mg omeprazole dose, a few subjects have minimal inhibition whereas others have more than 90% inhibition.<sup>267</sup> At 20 mg, inhibition is less variable (see Figs. 40-15D and 40-16). At 40 mg, marked inhibition of acid secretion is observed in the large majority of subjects (see Fig. 40-16). In Zollinger-Ellison syndrome, administering omeprazole in twice-daily dosing increases antisecretory effectiveness.<sup>267a</sup> The same is probably also true in other acid-peptic conditions, although data are surprisingly limited. Similar conclusions probably hold for the 15-, 30-, and 60-mg doses of lansoprazole,<sup>255,267</sup> although less data are

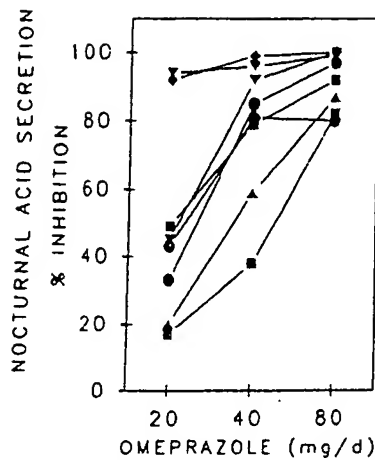


Figure 40-16. Dose response for omeprazole inhibition of nocturnal acid secretion. Acid secretion was determined during four night-time sessions for seven patients with duodenal ulcer; single doses were given at 8 A.M. of placebo or omeprazole at 20, 40, or 80 mg. Acid secretion was then determined between 9 P.M. and 6 A.M., with the data expressed as a percentage of control secretion. (Data from Shearman, D. J. C., Buckle, P. J., and Heitzel, D. J. The inhibition of nocturnal gastric acid secretion by omeprazole in patients with duodenal ulcer. *Scand. J. Gastroenterol.* 21(Suppl 118): 145, 1986.)

available, particularly to assess the consistency of responsiveness among individual subjects.

3. *PPIs effectively inhibit only stimulated parietal cells.* Because PPIs must be concentrated and activated in the acidic compartments of the parietal cell, they will only inactivate the  $H^+K^+-ATPase$  present in actively secreting membrane compartments. PPI effectiveness therefore depends on the degree of activation of acid secretion at the time of drug administration. Omeprazole action was markedly compromised in dogs if administered while secretion was inhibited by  $H_2$ RAs.<sup>268</sup> Although data in humans are limited, PPI efficacy is likely to vary considerably, depending on whether the patient is fasting, has taken an  $H_2$ RA, or has secretion activated by food, gastrin, or vagal pathways during the time the prodrug is circulating. PPIs will be most effective when taken with or shortly before meals; effectiveness is likely to be significantly compromised if taken during a prolonged fasting period.
4. *Rapid control of acid secretion* can be achieved using higher doses of a PPI, or more frequent administration (i.e., three or four doses of 20 mg of omeprazole in the first 24 hours). Continuing  $H_2$ RAs during a transition period to a PPI will be counterproductive. Combination therapy with  $H_2$ RAs is never appropriate: if greater antisecretory efficacy is required, the PPI should be administered in higher, divided doses.
5. *Administration of PPI via nasogastric tube,* although not an approved route, is likely to be effective. The bioavailability of omeprazole or lansoprazole when administered via nasogastric tube is comparable to oral dosing.<sup>269, 265a</sup> Capsules need to be opened and the enteric-coated granules administered via the tube, with extra volume and flushing used to avoid clumping. A solution of low pH (citric juice or cola) may be advisable to reduce premature dissolution of the granules.

The granules should not be crushed. Efficacy of PPI may be compromised by delayed gastric emptying of solids to the extent the emptying of granules is delayed.

Bolus intravenous administration to fasting subjects produced a lesser degree and shorter duration of acid inhibition, compared to when acid secretion is stimulated. In gastrinoma patients undergoing surgery, intravenous omeprazole in doses of 60 mg every 12 hours effectively controlled acid secretion.<sup>270</sup> Therefore, the critical factor is the degree of activation of the parietal cell. In unstimulated or inhibited parietal cells, the acidic compartment is collapsed and unable to trap and activate the PPI. Therefore, the majority of pumps remain unblocked, and the duration of inhibition will be short.

In an ICU setting with fasting patients, intravenous omeprazole is most effective when given by continuous infusion. An initial dose of 8 to 10 mg/hr is necessary to induce maximal inhibition of acid secretion.<sup>271</sup> Over a 3-day period, antisecretory control can be maintained with a reduced omeprazole dose, whereas increasing doses of  $H_2$ RAs are required.<sup>271</sup> Intravenous use of PPIs is not an FDA-approved route of administration. However, in patients without gastric retention, a nasogastric route of administration appears a reasonable alternative, although very limited data are available to guide management.<sup>271b</sup> The dose necessary to achieve secretory control has not been established; doses in the range of 20 mg every 6 hours may be necessary in fasting patients. Monitoring gastric pH will provide the best gauge of therapy.

## Antacids

Antacids containing aluminum and magnesium hydroxide effectively heal ulcers. However, the obvious conclusion that antacids heal ulcers solely by neutralizing gastric acid may not be correct, in part because the administered antacid buffering capacity poorly predicts ulcer healing. Furthermore, in animal models, antacids protect gastric mucosa against acute chemical injury in a fashion independent of buffering acid. Hypothesized mechanisms for these acid-independent actions of antacids overlap with those proposed for sucralfate.<sup>2, 84</sup> Aluminum complexes may be the shared property; aluminum hydroxide binds growth factors, enhances EGF binding to experimental ulcers, possibly serving to deliver growth factors to injured mucosa, and may have other cytoprotective actions.<sup>2, 84</sup> Antacids promote angiogenesis in injured mucosa.<sup>272</sup> They also bind bile acids and inhibit pepsin activity.<sup>273</sup> Heavy metals are well known to suppress—but generally not eradicate—*H. pylori*. It is unclear which, if any, of these actions facilitate peptic ulcer healing.

**Adverse Effects of Antacids.** Antacid side effects reflect the quantity consumed and the duration of therapy (see Table 40-5). Magnesium-containing antacids cause diarrhea and hypermagnesemia, the latter only being a significant problem in the presence of renal insufficiency. Antacids may also contain considerable sodium, and sodium overload can occur in susceptible patients. Ingestion of large amounts of calcium and absorbable alkali, particularly calcium carbonate, can lead to hypercalcemia, alkalosis, and renal impairment—the so-called milk-alkali syndrome.<sup>274</sup> Calcium-containing antacids also stimulate acid and gastrin secretion,<sup>275</sup> thereby inducing

"acid rebound."<sup>276</sup> Aluminum absorption and effects on mineral metabolism are discussed subsequently.

### Sucralfate

Sucralfate (Carafate) is a sulfated polysaccharide, sucrose octasulfate, complexed with aluminum hydroxide. It prevents acute, chemically induced mucosal damage and heals chronic ulcers without altering gastric acid or pepsin secretion or significantly buffering acid.<sup>277, 185</sup> Parallel with aluminum-containing antacids, sucralfate also stimulates angiogenesis and formation of granulation tissue,<sup>2</sup> possibly due to growth factor binding. Sucralfate also binds to the injured tissue, thereby possibly delivering growth factors and reducing access of pepsin and acid. Although aluminum hydroxide mediates some actions, the sucrose octasulfate moiety may also play a role by contributing sulfhydryl groups to reduce oxidant damage to epithelial cells. The binding of this agent to the ulcer base is enhanced at a pH below 3.5, leading to the recommendation that the drug be administered 30 to 60 minutes before meals. Sucralfate has been found to suppress *H. pylori* and inhibit acid secretion in *H. pylori*-infected DU subjects.<sup>46</sup> No data are available to test the relevance of this action by comparing ulcer healing in *H. pylori*-positive versus *H. pylori*-negative DU.

**Adverse Effects of Sucralfate.** Sucralfate has minimal untoward effects.<sup>183</sup> It can bind other drugs (see Table 40-5) if taken simultaneously, although the clinical consequences are minor.

### Aluminum and Mineral Metabolism with Sucralfate and Antacids

Significant absorption of aluminum occurs from several antiacid formulations.<sup>277</sup> Daily consumption for 4 weeks of doses as low as 120 mmol of antacid tablets increases serum and urinary aluminum levels.<sup>278</sup> A therapeutic dose of sucralfate contains about 0.8 g of aluminum, and the aluminum absorption is comparable to that seen with antacids.<sup>279</sup> Aluminum is readily excreted by normal kidneys; urinary levels are elevated for 1 to 3 weeks after discontinuing therapy,<sup>280-282</sup> and the body burden of aluminum appears to be eliminated within a few weeks after discontinuing therapy. However, significant retention occurs with renal failure;<sup>240</sup> neurotoxicity and brain deposition of aluminum can develop with antacids<sup>283</sup> or sucralfate.<sup>185, 284</sup> Even in subjects with normal renal function, simultaneous consumption of citric acid enhances absorption of aluminum by 50-fold, resulting in considerable elevations in serum aluminum concentration.<sup>278, 284</sup> It is likely that citric acid produces similar enhancement of aluminum absorption from sucralfate. To avoid enhanced aluminum absorption especially in the setting of renal failure, it is advisable to avoid combining antacids or probably sucralfate with foods or other agents that contain citric acid.

The extent and consequences of aluminum deposition in tissues with sustained use of either class of agents have not been defined, but the possibility of significant aluminum retention in the presence of normal renal function is remote. Although aluminum deposits have been reported in brain

tissue in Alzheimer's disease, evidence points against significant aluminum deposition in brain or a role for this metal in pathogenesis.<sup>285-287</sup> However, more rigorous investigation of tissue aluminum is required in humans before firm conclusions can be reached.

Aluminum hydroxide blocks intestinal absorption of phosphate; in two weeks of therapy with moderate doses, significant hypophosphatemia can develop, especially if the patient is on a low phosphate diet or is phosphate depleted for other reasons.<sup>288</sup> Sucralfate also binds phosphate, leading to similar theoretical consequences; and combining sucralfate and antacids can potentially amplify these effects.<sup>282</sup> With prolonged phosphate depletion, mineral metabolism is disrupted, urinary and fecal excretion of calcium are increased, and osteoporosis, osteomalacia, and pathologic bone fractures can develop.<sup>28, 289</sup>

### Bismuth

Several forms of bismuth have been used, including colloidal bismuth subcitrate (CBS), also known as tri-potassium dicitrato bismuthate (DeNol), and bismuth subsalicylate (BSS, Pepto-Bismol). Neither is approved for peptic ulcer therapy in the United States. BSS is a insoluble complex, with 30 mL containing 258 mg of salicylate and 303 mg of bismuth.<sup>290</sup> At a pH less than 3.5, hydrochloric acid reacts with BSS, forming bismuth oxychloride and liberating salicylate, which is readily absorbed. CBS is a complex bismuth salt that also forms bismuth oxychloride as the complex dissolves in hydrochloric acid. An elevated gastric pH may interfere with solubilization of bismuth compounds in the stomach. In the colon, bismuth salts reacts with hydrogen sulfide to form bismuth sulfide, which blackens the stools.<sup>290</sup> Presumably the free bismuth is responsible for the biologic actions. Ranitidine bismuth citrate (RBC) has been approved for treatment of *H. pylori*-positive peptic ulcer; RBC shares the properties of other bismuth salts in enhancing antibiotic cure of *H. pylori* infection, and ranitidine inhibits acid secretion.<sup>291</sup>

The venerable status of bismuth as therapy for dyspepsia has been adorned with numerous hypotheses regarding mechanisms for ulcer healing. Bismuth does not inhibit or neutralize gastric acid, although effects on acid secretion in DU should be examined in light of findings with sucralfate.<sup>46</sup> Pepsin activity but not pepsin secretion is inhibited by CBS.<sup>292</sup> Bismuth from CBS may also bind to ulcer craters.<sup>293, 294</sup> Macrophages, recruited to the edge of the ulcer crater in CBS-treated rats,<sup>293</sup> may promote healing. CBS has been reported to increase mucosal prostaglandin production and mucus and bicarbonate secretion. The subsalicylate salt has received too little study to determine its antiulcer properties.<sup>290, 295</sup> Although salicylate is absorbed, this nonacetylated form lacks the damaging effects of acetylated salicylate (aspirin). Heavy metals frequently exhibit antimicrobial activity, and the most dramatic action of bismuth, including BSS, CBS, and RBC, is the suppression of *H. pylori*<sup>296</sup> (see Chapter 39). Preliminary studies indicate that bismuth is not effective in *H. pylori*-negative ulcers, suggesting the healing efficacy of bismuth reflects *H. pylori* suppression.

**Adverse Effects of Bismuth.** The primary concern with bismuth compounds is bismuth absorption resulting in bismuth intoxication, which was a clinical problem particularly when



bismuth subgallate was used for prolonged periods at high dose. Bismuth absorption varies with the specific form of bismuth; absorption is much greater with CBS than with BSS or bismuth subnitrate.<sup>296, 297</sup> Furthermore, co-administration of H<sub>2</sub>RAs increases bismuth absorption from CBS but apparently not from BSS or bismuth subnitrate.<sup>298</sup> At the end of 6 weeks of therapeutic doses of CBS, serum bismuth concentrations are elevated.<sup>299</sup> An occasional patient will have serum bismuth levels approaching the pretoxic range of 50 ng/mL;<sup>299</sup> and following a single dose of CBS, peak plasma concentrations of 100 ng/mL were reached in 9 of 16 subjects.<sup>296</sup> However, significant clinical toxicity has not been reported in clinical trials with CBS or BSS.<sup>296, 299</sup> A body burden of bismuth does accumulate, and urine bismuth levels are somewhat elevated for up to 3 months after termination of an ulcer treatment regimen.<sup>300</sup> Because renal failure interferes with bismuth excretion, bismuth should be avoided or serum bismuth levels monitored when treating patients with renal failure.<sup>299</sup>

## Prostaglandins

Prostaglandins, particularly of the E and I group, inhibit acid secretion by selectively reducing the ability of the parietal cell to generate cyclic adenosine monophosphate in response to histamine (see Chapter 38). Prostaglandin receptors act by means of an inhibitory guanosine triphosphate binding protein of adenylate cyclase to produce this effect.<sup>301</sup> Prostaglandins also enhance mucosal defense mechanisms. When these two actions were recognized, enthusiasm was generated over the therapeutic prospects for common peptic ulcers, a promise that did not materialize. Naturally occurring prostaglandins are unstable, being metabolized primarily by hydroxylation at the 15 position on the eight-carbon side chain. Therefore, analogues were synthesized with modified structure on this side chain to provide resistance to degradation.

Several prostanoids have been tested for peptic ulcer healing; only misoprostol (Cytotec) has been approved for use in the United States for prevention of NSAID-induced GU. Misoprostol is a 15-deoxy-15-hydroxy-16-methyl analog of prostaglandin E<sub>1</sub>; it shares the properties of other E type prostaglandins, displaying moderate inhibition of basal and food-stimulated acid secretion in humans.<sup>302</sup> Topical action appears critical in prostaglandin action; oral administration gives greater antisecretory efficacy and fewer side effects than systemic administration.<sup>303</sup>

**Adverse Effects of Misoprostol.** The most frequent side effects of the E type prostanoids are crampy abdominal pain and diarrhea, which are dose-dependent effects.<sup>304, 305</sup> Diarrhea occurred in 3% to 39% of patients taking a 200- $\mu$ g dose of misoprostol four times a day, with the range reflecting trial design and the definition of diarrhea.<sup>304, 305</sup> Diarrhea is often mild and transient and may respond to a temporary reduction in dose. In clinical trials, usually less than 5% of subjects drop out because of diarrhea. However, in clinical practice these side effects interfere with compliance in many patients. The diarrhea is less with 200  $\mu$ g twice daily, and initiating therapy with this lower dose can be helpful.

Prostaglandins of the E group are generally uterotrophic; misoprostol, 400  $\mu$ g, was given to 35 pregnant women the night before they were to undergo elective abortion, and this

dose induced bleeding or cramps in 10%.<sup>304, 306</sup> Misoprostol is clearly contraindicated in women of childbearing potential who are not on contraception. All patients should be informed of this risk, to minimize the drug being inadvertently given by the patient to a pregnant woman.

## Drug Interactions with Antiulcer Drugs

**Altered Absorption.** As a result of intraluminal binding, antacids and sucralfate decrease absorption of a number of drugs (see Table 40-5).<sup>307, 308</sup> It is best to advise separation of consumption of antacids and other drugs by an hour. Bismuth may have the same effect, but data are limited.<sup>296</sup> Antisecretory agents, by increasing intraluminal pH, can alter drug absorption. The effect of antisecretory agents on absorption of food-bound vitamin B<sub>12</sub> can be quite dramatic.<sup>309, 310</sup> The effect appears to be mediated by the increase in pH and resultant decrease in peptic activity, rather than inhibition of intrinsic factor secretion.<sup>241</sup> The absorption of iron and calcium can also be compromised, although clinical consequences are minimal.

Dissolution of some drugs, particularly weak bases, will be decreased with gastric neutralization. The consequences depend on the specific drug and its preparation; for example, decreased dissolution of ketoconazole, a weak base, significantly decreases absorption.<sup>249</sup> Alternatively, the absorption of bismuth from CBS is increased, presumably because decreased gastric acidity increases free bismuth concentrations.<sup>298</sup> Acid-secretory inhibition can decrease the absorption of weak acids from the stomach and increase absorption of weak bases. For example, secretory inhibitors will reduce uptake into gastric mucosa of weak acid NSAIDs, such as aspirin, and decrease superficial damage. However, gastric absorption is usually modest compared with intestinal absorption, and systemic effects override this sparing of gastric mucosa.

**Drug Interactions by Means of Cytochrome P450.** Cimetidine, omeprazole, and, to a lesser extent, ranitidine inhibit members of the cytochrome P-450 superfamily of mixed function oxidases, thereby interfering with certain compounds metabolized by these phase I reactions (i.e., metabolism by CYP-dependent monooxygenase enzymes). Lansoprazole and pantoprazole are also metabolized by cytochrome P-450.<sup>256, 257, 261, 311</sup> so that drug interactions must be carefully evaluated for each PPI family member. Several features of cytochrome P-450 metabolism are important with respect to the antiulcer drugs:<sup>241, 259</sup>

1. Effects are dose and time dependent. Generally, 3 to 5 days are needed to reach maximal inhibition of drug metabolism, although effects can be delayed.
2. Interactions are highly variable among individuals, especially among elderly subjects. Importantly, data obtained from *in vitro* studies or the mean of data obtained studying a small sample of healthy subjects may not predict the magnitude of drug interaction in a given patient with multisystem disease being treated with several medications. Three-way drug interactions can produce unexpected results.
3. The CYP superfamily is composed of three major fami-

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**Editors:**

**MARVIN H. SLEISENGER, M.D.**

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San Francisco VA Medical Center;  
Professor of Medicine  
University of California, San Francisco  
San Francisco, California

**JOHN S. FORDTRAN, M.D.**

Chief, Department of Internal Medicine  
Baylor University Medical Center  
Dallas, Texas

*With a Foreword by Thomas P. Almy, M.D.*

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**Color Section Editor:**

**JOHN P. CELLO, M.D.**

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University of California, San Francisco  
Chief of Gastroenterology  
San Francisco General Hospital  
San Francisco, California

# Chapter 30

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ANDREW H. SOLL

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Peptic ulcers are defects in the gastrointestinal (GI) mucosa extending through the muscularis mucosae that persist as a function of the acid/peptic activity in gastric juice. In two prior editions, treatment of this topic was based on the assumption that duodenal ulcer (DU) reflected a heterogeneous set of disorders, each resulting in a hole in the mucosa. In light of present data, it appears that there are two *common* forms of peptic ulcer: ulcers associated with the organism *Helicobacter pylori* and ulcers associated with consumption of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin. The challenge is to establish the causal nature of these associations, to elucidate the underlying pathophysiologic mechanisms and therapeutic implications, and to define the subsets of peptic ulcer that occur by other mechanisms. The chapters on DU and gastric ulcer (GU) have been merged; although these entities share many common features and therapies, they remain distinct in several respects. Following the same rationale, NSAID-induced ulcers and stress ulcer have also been included.

### NORMAL ACID SECRETION AND MUCOSAL DEFENSE

#### Regulation of Acid Secretion

The regulation of acid secretion (see Ch. 27) reflects an intricate balance of input from neural, endocrine,

paracrine, and autocrine pathways and involves both stimulatory and inhibitory mechanisms. Acetylcholine is the primary mediator for the neural pathway; however, mucosal nerves also contain multiple other transmitters that may be of physiologic importance. Gastrin is the primary endocrine transmitter. The paracrine pathway is the most difficult to study, since these transmitters are released locally and act locally. For example, it was only with the development of the histamine  $H_2$  receptor antagonists that the importance of the paracrine role of histamine became clear. Several paracrine inhibitors are present in the mucosa, with somatostatin being the most likely candidate to play an important physiologic role. Lastly, three autocrine inhibitors are also generated in the oxyntic (acid-secreting) mucosa: adenosine, prostaglandins, and transforming growth factor  $\alpha$ ; their role in the normal physiology of acid secretion remains to be defined. These regulatory pathways impinge not only on the parietal cell but also on the histamine enterochromaffin-like (ECL) cell and on the somatostatin cell to control the release of histamine and somatostatin, respectively.<sup>1</sup>

An obvious emerging theme is that the control mechanisms regulating acid secretion entail redundant, overlapping circuits. Although these multiple mechanisms may not all be physiologically important, this redundancy probably exists to provide multiple circuits for more precise control and/or to provide backup systems so that control is not lost if one system fails. Although the details

rences are influenced by prior ulcer treatment (see Duodenal Ulcer Recurrence: Does the Initial Therapy Matter?). Whether the specific patient population or ulcer location (DU versus distal or proximal GU) influences the putative fading of ulcer disease over time remains unclear. Although ulcer disease may fade in a fortunate subset of patients, others continue to experience symptoms, ulcers, and complications over a prolonged period; therapeutic choices would be influenced by the ability to predict the natural history for a given patient.

## MEDICAL TREATMENT

### The Data Base for Therapeutic Decisions

Double-blind, randomized clinical trials, utilizing endoscopy to document the status of an ulcer crater during therapy, provide a data base for rational decisions regarding management of peptic ulcer. These trials are not perfect tools and caution is necessary extrapolating this knowledge to clinical practice.<sup>553</sup> These trials have been performed on selected patient populations and data generally collected at referral centers; therefore, these patients will not necessarily be typical of community practice experience. One variable is the length of time it takes for patients to seek medical care and to be referred to and arrive at the center conducting the trial; some ulcers spontaneously heal in two to four weeks and those persisting long enough for the patients to arrive at tertiary centers are a more refractory variety of ulcer.

**WHAT IS HEALED?** Since symptoms often provide misleading information about ulcer status, endoscopy has become the gold standard of ulcer healing. However, assessing healing is somewhat subjective and classifying erosions or duodenitis is problematic. With the focus of endoscopy on the status of the crater, clinical aspects receive less attention. The goals of therapy in clinical practice are not only to heal ulcer craters but also to relieve symptoms, prevent complications, minimize ulcer recurrences, reduce untoward consequences of diagnosis and therapy, and minimize the costs of medical care and the time lost from work. The benefit to the unselected patient of ensuring that all DUs have healed and remain healed is controversial. However, ulcer healing *per se* may be an appropriate goal for GU patients, at least until carcinoma has been confidently excluded.

### Factors Influencing Ulcer Healing

**PLACEBO AND THERAPEUTIC RESPONSES.** As with most aspects of medicine, the natural history of the disease process often has a greater impact on outcome than the therapy prescribed. The natural history of peptic ulcers varies from rapid spontaneous healing to refractory ulceration persisting for months despite full-dose antisecretory therapy. The outcome of trials and the conclusions regarding the apparent potential benefit of a drug will be influenced by the proportion of slow-healing and fast-healing ulcers, as reflected in the placebo healing rates.

DU healing on placebo therapy varies from 24 to 75 per cent (see Fig. 30-19). A highly significant negative correlation is evident between placebo healing rates and the incremental improvement in healing produced by active drug (see Fig. 30-19). Establishing efficacy may be difficult when placebo healing rates are high, as they were in the early cimetidine studies from the United States.<sup>554</sup>

Several variables influence ulcer healing; these factors, such as NSAID use or cigarette smoking, usually have a much greater relative impact on spontaneous or placebo healing than healing in response to an active drug.<sup>555</sup> The impact of other factors is quite variable between studies, reflecting patient selection, sample size, and the probability that several variables are operating simultaneously.

Placebo therapy produces surprisingly high healing rates that are often credited to extrinsic factors rather than the placebo itself. However, placebos can alter pain perception and may alter ulcer healing compared with no therapy.<sup>556</sup> The mechanism by which placebos relieve pain is not clear. Placebo administration does not alter meal-stimulated acid output.<sup>557</sup> Most studies have allowed supplemental antacids as needed for pain, but low-dose antacid consumption hastens ulcer healing and probably increases apparent "placebo" healing rates.

**SMOKING.** Smoking is a risk factor for ulcers and their complications (see Potential Risk Factors and Associations). In addition, clinical trials provide strong evidence that smoking impairs ulcer healing and promotes recurrences. Batterman and Ehrenfeld in 1949<sup>558</sup> recognized that nonsmokers and ex-smokers responded better than active smokers to antacid therapy, thereby highlighting the deleterious, but reversible, effects of smoking on the natural history of ulcer disease. Impaired healing of both GU and DU<sup>305, 462, 555, 559-562</sup> and enhanced ulcer recurrence<sup>262, 555, 563, 564</sup> in smokers compared with nonsmokers have been found in numerous controlled trials, with rare exception.<sup>565</sup> The differences between smokers and nonsmokers are most dramatic in placebo-treated groups (see Fig. 30-22B). Active therapy with most drugs ( $H_2$  blockers, prostaglandins, antacids, sucralfate, colloidal bismuth, and so on) generally reduces—but does not always eliminate—the deleterious effects of smoking. Inhibiting nocturnal secretion may be particularly important in smokers as opposed to nonsmokers.<sup>566</sup> Lam argues that misoprostol<sup>562</sup> and sucralfate<sup>567</sup> more effectively reverse the deleterious effects of smoking on healing than do antisecretory agents. However, the advantages for one specific modality remain controversial. Underlining the impact of cigarettes, nonsmoking was a more important predictive factor in ulcer healing<sup>555</sup> and ulcer recurrence<sup>308</sup> than was treatment with  $H_2$  blockers. Importantly, the ulcer risk with smoking correlates with the quantity of cigarettes smoked; the risk is modest with fewer than 10 cigarettes smoked daily, whereas in those who smoke more than 30 cigarettes daily, healing is markedly impaired and recurrences in 3 months can reach 100 per cent.<sup>262, 305, 568, 569</sup>

**NSAIDS.** Since NSAIDs cause virgin ulcers and exacerbate an ulcer diathesis (see Peptic Ulcer and Nonsteroidal Anti-inflammatory Drugs), it is not surprising that NSAIDs also delay ulcer healing. NSAID consumption may be occult,<sup>570, 570a</sup> prompting caution regarding "negative" drug histories. Ulcers developing during NSAID

use generally heal readily on any active antiulcer therapy if NSAIDs are discontinued. Although spontaneous healing and healing on various therapies do occur even with continued NSAID use,<sup>225, 566</sup> the efficacy of moderate antisecretory therapy does appear compromised in this setting (see NSAID-Induced Ulcers; Treatment and Prevention).<sup>259, 260</sup>

**ACID SECRETION.** The extent to which pretreatment levels of acid secretion predict ulcer healing or recurrences remains controversial. Acid hypersecretion has been proposed as a factor impairing healing or promoting recurrences,<sup>566, 569, 571</sup> although others dispute this association. Increased serum pepsinogen I has also been correlated with enhanced recurrence rates,<sup>148, 571</sup> although whether this reflects increased secretory mass, *H. pylori* infection, degree of inflammation, or some other variable is unclear.

In gastrinoma, clear goals can be established for the inhibition of acid secretion. However, in ordinary peptic ulcer drawing correlations between the magnitude of inhibition of acid output and ulcer healing or recurrence on maintenance therapy has been problematic.<sup>572</sup> Meta-analysis was needed to demonstrate that the magnitude of inhibition of acid secretion predicts duodenal and—to a much lesser extent—gastric ulcer healing (see Ulcer Healing Correlates With the Degree and Duration of Inhibition of Acidity). Variability among individuals may reflect important heterogeneity in pathogenic mechanisms and drug responses; residual acid secretion during antisecretory therapy may have critical importance only in a subset of peptic ulcer subjects.

**INPATIENT VERSUS OUTPATIENT ULCERS.** Patients who first develop ulcers or ulcer complications while in the hospital experience more severe complications and respond poorly to medical and surgical therapy (see Stress Ulcer). Distinguishing this type of ulcer disease is crucial.

#### OTHER CORRELATES OF ULCER HEALING

**Ulcer Size.** A venerable radiologic study indicated that large and small GUs heal at the same rate on antacids, about 3 mm per week.<sup>573</sup> Therefore, larger ulcers will require more time to heal. Ulcer size, especially when a broad range is considered, has been shown to influence healing rates for GU.<sup>259, 574</sup> Obviously, giant ulcers require more time to heal on antiulcer therapy than do smaller ulcers. Ulcer size has been a variable in some but not all studies of DU.<sup>566, 575</sup>

**The Predictive Value of the Prior History.** The patient's past ulcer history will be one of the best predictors of future behavior. For example, patients with a history of complications have an increased chance of future complications. Ulcers refractory to initial healing are likely to rapidly recur and ulcers that have recurred frequently are likely to continue to do so. A long duration of symptoms leading to presentation suggests an ulcer that is unlikely to heal spontaneously or respond readily to antiulcer therapy.

**Age and Sex.** Young women may heal better than young men.<sup>555</sup> The effect of age is variable. Disease with an onset in youth and with a positive family history may be associated with poor healing.<sup>569, 576</sup> On the other hand, ulcers in older patients may heal more slowly than in younger patients.<sup>555, 573, 577–579</sup> Older patients are also more

likely to bleed and re-bleed, to require more transfusions, and to have a prolonged hospital stay, probably due to co-morbidity.<sup>448, 449</sup>

**Other Ulcer Variables.** Prepyloric ulcers and pyloric channel ulcers have been reported to heal more slowly than DU,<sup>535, 580</sup> although these conclusions are controversial. Stenosis or deformity of the duodenal bulb, detected at endoscopy, predicts impaired healing<sup>560, 581</sup> and enhanced relapse rates.<sup>582, 583</sup> Decreased blood flow in the margin of both DU<sup>196</sup> and GU<sup>195</sup> has been associated with slow healing. Patients with simultaneous DU and GU may also have delayed healing and a more complicated course.

**Alcohol and Beverage Consumption.** Many patients are told to stop drinking alcohol; however, there are no solid data indicating that *modest* alcohol consumption retards healing.<sup>555, 584</sup> On the contrary, such modest alcohol intake may even promote ulcer healing.<sup>555</sup> Alcohol abuse, on the other hand, interferes with patient compliance and ulcer healing.<sup>569, 575</sup> Wine, beer, coffee, decaffeinated coffee, and many other beverages are also strong acid secretagogues (see Potential Risk Factors and Associations: Diet). Consuming a beer at bedtime will stimulate near maximal acid output while providing only modest buffering capacity that will be rapidly emptied. One can speculate that this habit, if sustained, might exacerbate an ulcer diathesis or esophageal reflux and may weaken inhibition of acidity by  $H_2$  blockers given with the evening meal.<sup>585</sup> However, recommending elimination of beverages that are strong secretagogues would restrict a patient to little more than bread and water. Moderation in the consumption of strong secretagogues, especially on an empty stomach or at bedtime while not on antisecretory therapy, is an appropriate compromise.

**Diet.** Although certain foods produce dyspepsia, there is no evidence that specific foods alter ulcer healing or recurrences. Investigators, appropriately from Texas, reported that red and black peppers cause *acute* gastric mucosal injury comparable to that produced by aspirin.<sup>586</sup> Whether ingestion of pepper or other spices or foods impairs ulcer healing is doubtful, but avoidance of foods that produce dyspepsia is safe advice for an ulcer patient.

Before the advent of specific therapy for peptic ulcer, dietary manipulations were utilized, although support for their effect on healing was scant.<sup>587</sup> Frequent feedings, justified on the basis that small meals cause less gastric distention, may lead instead to more sustained stimulation of acid secretion. As with alcohol or other beverages, bedtime snacks stimulate nocturnal acid secretion. Milk, because of its soothing nature, was a mainstay of therapy until it was shown to be a strong secretagogue, largely because of its calcium and protein content.<sup>588</sup> Milk stimulates more acid secretion than it buffers and is not an effective antacid. However, milk may reduce acute acid-induced damage in rats<sup>589</sup> and protect against cysteamine-induced acute DU in mice.<sup>590</sup> Furthermore, four days of milk consumption decreased histamine-stimulated acid secretion in rats.<sup>590a</sup> Human milk contains potentially protective factors, including growth factors similar to epidermal growth factor, surface active phospholipids, and prostaglandin  $E_2$ . Thus, it is possible that milk has antiulcer actions that override stimulation of acid secretion. However, in a limited study in which patients on

cimetidine (1 gm daily) were randomized to a normal diet or a diet supplemented with 2 liters of milk daily,<sup>591</sup> ulcers healed in 78 per cent of patients on the normal diet compared with 53 per cent of patients on the milk-supplemented diet, indicating no benefit to ulcer healing in humans. Spiro<sup>592</sup> argues that since milk and a bland diet may produce subjective benefit in patients with dyspepsia, their use should not be discarded solely because of a lack of scientific validation. However, ulcer patients should be cautioned that milk is neither an antacid nor specific therapy for their ulcer.

**PSYCHODYNAMIC FACTORS INCLUDING THE PHYSICIAN-PATIENT RELATIONSHIP.** Psychosocial factors and the clinical setting may influence not only perception of symptoms but also ulcer healing rates. The physician-patient relationship may be another important variable; one study found that the duration of pain during a recurrence varied significantly among patients treated by different physicians.<sup>593</sup> Stressful life situations, such as occupational, financial, and family problems, have been reported to be more frequent in patients with DU that required longer than six weeks to heal.<sup>594</sup>

Psychodynamic factors require assessment during the initial evaluation of a patient with chronic disease; insight into these factors may guide the diagnostic as well as the therapeutic approach. Since there is no consensus regarding either the importance of psychosomatic mechanisms in pathogenesis or the impact of psychotherapy on the course of ulcer disease, psychotherapeutic intervention should be reserved for those patients in whom it is indicated on independent grounds. Because psychodynamic factors are frequently present in patients presenting with chronic abdominal pain, careful psychosocial evaluation is indicated for most, if not all, patients presenting with ulcer or nonulcer dyspepsia.

## Antiulcer Pharmacology

There are three modes by which acid secretion can be inhibited: antagonism of receptor interactions, blockade of cell activation, and inhibition of the  $H^+, K^+$ -ATPase.

### $H_2$ RECEPTOR ANTAGONISTS

Four  $H_2$  receptor antagonists, cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid), have been approved by the FDA for use in the United States (Table 30-5). These agents are specific antagonists that inhibit acid secretion by blocking histamine  $H_2$  receptors on the parietal cell.

**Structures.** Cimetidine shares the imidazole ring structure of histamine itself. Ranitidine is chemically distinct, based on a furan ring structure. In contrast, famotidine utilizes a thiazole ring structure. The side chains that confer  $H_2$  receptor specificity are unique on each of these compounds. Nizatidine combines the thiazole ring of famotidine with the side chain of ranitidine.<sup>595, 596</sup>

**Absorption and Distribution.** All four drugs are well absorbed after oral dosing. Absorption of these drugs is inhibited by 10 to 20 per cent by concomitant antacids, whereas food does not reduce absorption. Peak serum concentrations are achieved after one to three hours. All four drugs are distributed to most body organs, including

TABLE 30-5.  $H_2$  BLOCKERS

| DRUG       | SERUM HALF-LIFE | RELATIVE POTENCY | EQUIVALENT DOSE (mg) | STANDARD DAILY DOSE (mg) | MAINTENANCE DOSE (mg) |
|------------|-----------------|------------------|----------------------|--------------------------|-----------------------|
| Cimetidine | 1.5-2.3 h       | 1                | 600-800              | 800 hs<br>(400 b.i.d.)   | 400 hs                |
| Ranitidine | 1.6-2.4 h       | 4-10             | 150                  | 300 hs<br>(150 b.i.d.)   | 150 hs                |
| Nizatidine | 2.5-4 h         | 20-50            | 20                   | 300 hs<br>(150 b.i.d.)   | 150 hs                |
| Famotidine | 1.1-1.6 h       | 4-10             | 150                  | 40 hs<br>(20 b.i.d.)     | 20 hs                 |

Modified from Feldman, M. and Burton, M.E. Histamine<sub>2</sub>-receptor antagonists. Standard therapy for acid-peptic diseases. N. Engl. J. Med. 323:1672, 1990.

cerebrospinal fluid; they also cross the placental barrier and are excreted in breast milk.<sup>595, 597</sup> The distribution of cimetidine in cerebrospinal fluid appears to be increased in liver failure,<sup>595, 598</sup> prompting caution regarding CNS side effects in this setting.

**Hepatic Metabolism.** All four drugs are eliminated by a combination of hepatic metabolism, glomerular filtration, and renal tubular secretion.<sup>595</sup> Bioavailability of cimetidine, famotidine, and ranitidine is reduced by 30 to 60 per cent by first-pass hepatic metabolism.<sup>595</sup> In contrast, bioavailability with intravenous dosing approaches 100 per cent, thereby justifying dose reductions with intravenous administration, depending on the goals of treatment. Since nizatidine undergoes little hepatic metabolism, bioavailability of nizatidine following oral dosing is 100 per cent. The half-life of cimetidine is prolonged with liver failure.<sup>598, 599</sup> Some authors advise dose reduction in the presence of significant hepatic dysfunction,<sup>599, 600</sup> while others advise a decrease in the dose only if renal failure accompanies severe hepatic disease.<sup>595</sup>

**Renal Excretion.** Renal clearance of all four agents is generally greater than accounted for by glomerular clearance, reflecting the importance of renal tubular secretion.<sup>595</sup> Cimetidine and ranitidine compete with creatinine for renal tubular secretion, so that these  $H_2$  blockers cause a slight elevation of creatinine. Since renal clearance is important for the elimination of all four agents, doses are generally reduced by 50 per cent in patients with moderate to severe renal failure.<sup>595</sup> Famotidine and nizatidine have the greatest dependence on renal clearance, so that their half-life is more prolonged with renal failure. The quantities of the  $H_2$  antagonists removed by peritoneal dialysis and hemodialysis are small and replacement doses are not necessary. Clearance is decreased in neonates and in the elderly, prompting recommendations to reduce the dose in persons over 75 years of age.<sup>595, 601</sup>

### ADVERSE EFFECTS OF $H_2$ RECEPTOR ANTAGONISTS

Three categories of adverse effects are considered (Table 30-6).<sup>602</sup> (1) The *toxic effects* reflect excess effects by means of their normal mechanisms. For the  $H_2$  blockers, toxic actions would reflect excess inhibition of acid secretion, as discussed subsequently. (2) *Side effects* reflect actions unrelated to the primary therapeutic action, such as those enumerated below. (3) Lastly, *drug interactions* are considered at the end of this section.



TABLE 30-6. ADVERSE EFFECTS FROM ANTIULCER THERAPY

| TABLE 33-3. ADVERSE EFFECTS OF H <sub>2</sub> BLOCKERS |   |            |   |          |
|--|---|------------|---|----------|
|  | H <sub>2</sub> BLOCKERS   | OMEPRAZOLE | SUCRALFATE  | ANTACIDS |
| I. Toxic effects                                       | <i>Hypochlorhydria:</i><br>Bacterial overgrowth<br>Hypergastrinemia<br>Altered absorption from alkalinization<br>Decreased absorption of divalent cations<br>Decreased B <sub>12</sub> absorption             |            |   |          |
| II. Side effects                                       | Antiandrogenic: cimetidine CNS reactions; headaches; immune modulation; cardiac conduction abnormalities; idiosyncratic hepatic injury; immune hypersensitivity reactions; thrombocytopenia; granulocytopenia |            | Aluminum absorption, phosphate depletion  |          |
| III. Drug interactions                                 |   |            |   |          |
| A. Absorption  | Intraluminal alkalinization, inhibits absorption (e.g., ketoconazole)   |            | <i>Intraluminal drug binding of:</i><br>Tetracycline, ciprofloxacin, isoniazid, chloroquine, warfarin, digoxin, phenytoin, quinidine, aspirin and other NSAIDs, cimetidine, ranitidine, ferrous sulfate, theophylline |          |
| B. P <sub>50</sub> mediated                            | <i>Cimetidine (&gt;&gt;ranitidine)</i><br>Warfarin, theophylline, phenytoin, diazepam, propranolol  |            | Diazepam, warfarin, phenytoin   |          |
| C. Excretion   | ↓ Renal tubular excretion of procainamide   |            |   |          |

The H<sub>2</sub> receptor antagonists are remarkably safe drugs. Summating short-term controlled trials, adverse reactions for cimetidine are not different from placebo.<sup>603</sup> Postmarketing surveillance studies have supported the safety profile of cimetidine.<sup>604, 605</sup> The other H<sub>2</sub> blockers appear to have the same excellent safety profile. However, a number of uncommon side effects have been reported with H<sub>2</sub> blockers, primarily as isolated cases or retrospective, uncontrolled series. However, causality cannot be established from the temporal association between drug use and an untoward effect, particularly when the clinical situation is complicated by serious medical illness and the use of multiple drugs.<sup>606</sup> In addition, no reasonable conclusions regarding causality can be drawn without drug rechallenge, which is rarely performed. Although differences exist among the H<sub>2</sub> blockers for certain side effects, the focus has been on cimetidine for a number of reasons: (1) the reporting of side effects is directly proportional to the clinical experience with a compound, (2) side effects are more commonly reported when the class of compounds is newly introduced, and (3) bias is created once a drug is linked to a putative side effect.<sup>606</sup> Therefore, in the absence of controlled comparisons, only limited conclusions can be drawn regarding the relative occurrence of uncommon side effects with the H<sub>2</sub> blockers.

**Antiandrogenic Effects.** Cimetidine can produce gynecomastia and impotence; however, these effects are dose- and time-dependent. Gynecomastia is rare with less than eight weeks of therapy at normal doses of cimetidine and has occurred in only 0.2 per cent of patients treated for 26 weeks.<sup>607</sup> The most convincing evidence that the putative antiandrogenic effects of cimetidine are clinically relevant are the findings that gynecomastia and impotence

occur in half of the men with hypersecretory disorders who undergo prolonged high-dose cimetidine therapy. Furthermore, when these patients were switched from cimetidine to ranitidine therapy, the gynecomastia and impotence gradually resolved,<sup>608</sup> indicating a true difference between H<sub>2</sub> blockers with prolonged use of high doses. Thus, although gynecomastia and/or impotence have been rarely reported in association with the other H<sub>2</sub> blockers,<sup>595, 609, 610</sup> clinical relevance remains questionable.

Evidence indicates that cimetidine produces antiandrogenic effects by antagonism of peripheral androgen receptors.<sup>595</sup> Hyperprolactinemia can occur with intravenous injection of 300 mg of cimetidine and with intravenous doses of ranitidine above 100 mg.<sup>595, 607</sup> However, neither drug given orally produces hyperprolactinemia or alterations in circulating testosterone, LH, or FSH levels.<sup>611</sup> These endocrine effects of H<sub>2</sub> blockers are reversible and have little clinical impact with normal doses even with prolonged use.

**Effects on the Immune System.** H<sub>2</sub> receptors appear to be present on suppressor T lymphocytes.<sup>612</sup> Several observations suggest that blockade of these receptors enhances immune function: enhanced cell-mediated immunity, enhanced responsiveness of peripheral blood lymphocytes to mitogenic stimulation,<sup>613</sup> and restoration of sensitivity following development of acquired tolerance<sup>612</sup> have been observed in patients on H<sub>2</sub> blocker therapy. Although further studies are needed, enhanced immune function in response to H<sub>2</sub> antagonists may have desirable effects, such as facilitating resolution of viral or other infections in immunocompromised hosts or improving clinical performance status in HIV-infected pa-



tients.<sup>612, 614</sup> However, deleterious effects may also result from H<sub>2</sub> receptor blockade, such as enhanced transplant rejection and enhanced autoimmune or allergic activity. Most of these studies were done with cimetidine, and it is possible that some of these immunomodulatory effects reflect a unique action of the imidazole ring rather than actions at H<sub>2</sub> receptors. Comparative data with other H<sub>2</sub> blockers are limited and conflicting on this point<sup>613, 615, 616</sup>; the relative efficacy and clinical significance of the actions of H<sub>2</sub> blockers on the immune system will be clarified only by further study.

Other uncommon reactions may be mediated by immune mechanisms, including polymyositis and interstitial nephritis reported with cimetidine.<sup>612, 617</sup> An immune complex rash<sup>618</sup> has been reported with ranitidine. Fever has been associated with both cimetidine and ranitidine, with a rechallenge supporting association with ranitidine therapy.<sup>619</sup>

**Hematopoietic Effects.** H<sub>2</sub> blockers have been implicated in rare cases of myelosuppression, thrombocytopenia, neutropenia, anemia, and pancytopenia.<sup>595, 620-623</sup> These cases are idiosyncratic, in that events are rare and unpredictable. H<sub>2</sub> blockers have been implicated in hemolytic anemia, although detailed studies in some of these cases have failed to find antidrug antibodies or hemolysis upon rechallenge,<sup>624</sup> underlining the need for caution in extrapolating from temporal association to causality. Complement-mediated immune mechanisms involving ranitidine have been implicated in Coombs-positive anemia.<sup>625</sup> Thrombocytopenia has also been linked to hypersensitivity to ranitidine, with cross-reaction with cimetidine reported<sup>626</sup> and refuted.<sup>627</sup>

In the setting of bone marrow transplantation, myelosuppression has been associated with H<sub>2</sub> blockers. For example, in about 5 per cent of 223 bone marrow transplantation cases treated with ranitidine, clinical evidence and the absence of other potential factors implicated ranitidine as the probable cause of myelosuppression.<sup>628</sup>

In summary, several mechanisms can potentially mediate the immune and hematopoietic effects of H<sub>2</sub> blockers: (1) idiosyncratic reactions of the immune hypersensitivity type, (2) idiosyncratic reactions occurring by unknown mechanism, (3) effects mediated by blockade of pharmacologically typical H<sub>2</sub> receptors, or (4) pharmacologic effects on target hematopoietic or immune cells independent of the H<sub>2</sub> receptor. In normal hosts, effects are rarely of clinical significance, but they may become clinically relevant if the immune or hematopoietic system is perturbed, such as following transplantation. Until adequate data are available, caution should be exercised in the use of H<sub>2</sub> blockers in patients in whom enhancing immune function would be deleterious, such as after transplantation or with autoimmune disorders.

**CNS Side Effects.** CNS symptoms, including confusion, restlessness, somnolence, agitation, headaches, and dizziness, have been reported with H<sub>2</sub> blocker therapy.<sup>606</sup> Hallucinations, focal twitching, seizures, unresponsiveness, and apnea have been implicated to occur if therapy is continued.<sup>629, 630</sup> CNS side effects from any H<sub>2</sub> blocker are quite uncommon during outpatient therapy. Mental status changes have been reported, particularly in the ICU in elderly patients with renal and/or hepatic dysfunction,<sup>629, 631, 632</sup> although the incidence of such symptoms

with H<sub>2</sub> blockers varies greatly among studies.<sup>606</sup> Age and multiple system failure predispose to CNS symptoms in the ICU setting, with this high background preventing firm conclusions regarding the risk of CNS side effects from H<sub>2</sub> blockers.<sup>606</sup> Proving exacerbation of "ICU-itis" by a single drug would require large, randomized controlled trials,<sup>606</sup> which have not been performed. CNS reactions usually occur within the first two weeks of therapy.<sup>606</sup> Cimetidine has been implicated as the most frequent cause of these CNS symptoms. However, CNS effects also occur with ranitidine and famotidine.<sup>595, 606, 632-634</sup> Ranitidine also has been reported to produce headaches, with positive rechallenge in a few cases.<sup>635</sup> Because of the inadequacy of the literature and the biases noted above, case reports and uncontrolled series suggest that all of the H<sub>2</sub> blockers uncommonly produce CNS effects; the relative impact of the different H<sub>2</sub> blockers remains uncertain.<sup>606</sup> Whether these adverse effects occur less frequently with continuous IV dosage remains to be established. The mechanisms producing these CNS effects have not been identified; interaction with cerebral H<sub>2</sub> receptors<sup>636</sup> is possible but unlikely because reactions are highly unpredictable rather than dose dependent.

**Hepatic Effects.** Transient, small increases in serum transaminases can occur with H<sub>2</sub> blocker therapy, especially with high intravenous doses, but these changes resolve during continued therapy.<sup>600, 637</sup> Very rare cases of acute hepatitis have been reported within two days to seven months after initiation of cimetidine or ranitidine treatment.<sup>600</sup> Only a few of these cases are associated with apparent immune hypersensitivity (rash, fever, eosinophilia); the other cases are probably due to an idiosyncratic response to a metabolite.<sup>600</sup> Generally the acute hepatitis is rapidly reversible after withdrawal of the agent; rechallenge has been positive in a few cases. However, because of the rarity of these reports and their occurrence in patients with other potential causes of hepatic injury causality remains uncertain in many cases. Clearly, none of the four H<sub>2</sub> blockers are hepatotoxic, but probably all four agents are capable of rare, idiosyncratic hepatic injury.<sup>600</sup> These events are too uncommon to justify the cost of serial monitoring of liver function. However, it might be prudent to check hepatic function about five days into high-dose intravenous therapy. If hepatitis does develop in a patient on H<sub>2</sub> blockers, immediate discontinuation of the drug is indicated. If H<sub>2</sub> blocker therapy needs to be continued, after resolution of the liver function abnormalities, one of the other three H<sub>2</sub> blockers should be selected and liver function carefully followed. Readministration of the same drug requires close monitoring. Contrary to early reports, H<sub>2</sub> blockers do not appear to alter hepatic blood flow significantly.<sup>600</sup>

**Cardiac Effects.** Sinus bradycardia, A-V block, prolongation of the Q-T interval, and sinus and cardiac arrest have occurred with the rapid infusion of H<sub>2</sub> blockers, although oral therapy has been also incriminated in producing cardiac effects.<sup>638-640</sup> H<sub>2</sub> receptors are present in the heart, and H<sub>2</sub> blockers do appear to slightly reduce heart rate and blood pressure during submaximal exercise. However, whether the significant adverse effects on sinus rhythm and conduction are due to cardiac H<sub>2</sub> receptors or other compound-specific effects is uncertain. Of interest, in a case report in which oral ranitidine

induced atrioventricular block, similar changes were not found with other  $H_2$  blockers,<sup>641</sup> indicating that ranitidine was active via an  $H_2$  receptor-independent mechanism. Possible risk factors for cardiac effects of  $H_2$  blockers include rapid IV infusions, high dosage, conditions such as renal or hepatic dysfunction that would alter clearance, and underlying cardiac disease.<sup>638-640, 642</sup> The degree to which these effects occur with continuous intravenous infusions remains to be established.

### OMEPRAZOLE

**Mechanism of Action.** Omeprazole is a substituted benzimidazole with a unique antisecretory action based upon inhibition of the parietal cell  $H^+$ ,  $K^+$ -ATPase, the pump responsible for acid secretion.<sup>643, 644</sup> This specific ATPase is present in the parietal cell membranes that line the apical surface and the tubulovesicles that fill the cytoplasm in the resting state. With stimulation, these tubulovesicles are transformed into secretory channels that drain into the lumen, thereby positioning the  $H^+$ ,  $K^+$ -ATPase for the job of secreting acid. The enzyme appears to be active in the tubulovesicles, but little acid is secreted because of low luminal concentrations of  $K^+$ , which are necessary for exchange with  $H^+$ . Crucial to the secretion of acid is the activation or insertion of a membrane channel for transport of  $K^+$   $Cl^-$ .<sup>645</sup>

Three features account for the unique action of omeprazole.<sup>643</sup> (1) Omeprazole is a weak base that is concentrated in the acid compartments of the parietal cell by pH partition. With a  $pK_a$  of 4.0, omeprazole rapidly permeates plasma membranes at physiologic pH. However, when it encounters the acidic environment of the tubulovesicles and canaliculi of the parietal cell, it becomes ionized and therefore trapped and concentrated in the acidic compartments that contain the  $H^+$ ,  $K^+$ -ATPase. (2) At acid pH omeprazole is converted from a prodrug to a sulfenamide intermediate with a reactive sulfhydryl group. This "on-site" activation accounts for the unique targeting of omeprazole's action. (3) Activated sulfenamide and sulfenic acid derivatives of omeprazole form a disulfide bond with cysteine residues on the  $\alpha$  chain of the  $H^+$ ,  $K^+$ -ATPase, thereby inactivating the enzyme.<sup>646</sup> This disulfide bond can be broken by reducing agents. However, in the parietal cell, the inactivation is essentially irreversible and accounts for the prolonged action of omeprazole. The recovery of acid secretion probably reflects the synthesis of new  $H^+$ ,  $K^+$ -ATPase; spontaneous reduction of the disulfide bond appears to account for at most a minor component of the recovery of enzyme activity.

**Formulation and Absorption.** Because omeprazole is acid-labile, it will be inactivated if permitted to dissolve in the acidic gastric juice. Therefore, with the oral preparation, enteric-coated granules are dispersed in the stomach; these granules do not dissolve until encountering a pH above 6 in the intestine. Following an oral dose of a buffered suspension, omeprazole is rapidly absorbed and peak plasma levels reached in 30 min; the half-life in the serum is one hour.<sup>647</sup> Absorption of the enteric-coated granules is slower, with peak concentrations occurring one to three hours after dosing and the drug detectable in serum for about eight hours (Fig. 30-23A).<sup>648</sup> This pharmacokinetic pattern underlines the conclusion that

the prolonged duration of omeprazole's antisecretory action reflects its irreversible inactivation of the parietal cell  $H^+$ ,  $K^+$ -ATPase, rather than a prolonged serum half-life. Bioavailability of omeprazole increases after five days of treatment,<sup>647, 648</sup> probably as a result of increased absorption of the acid-labile drug following full induction of the antisecretory effect or altered first-pass hepatic metabolism.

The effectiveness of omeprazole, at least when given by oral administration, reflects the area under the plasma concentration-time curve (AUC) rather than the peak serum levels of omeprazole (Fig. 30-23B).<sup>647, 649</sup> Administering omeprazole with food delays absorption of the drug but does not diminish the total absorbed dose and therefore should not diminish effective delivery of omeprazole to the parietal cell.

**Hepatic Metabolism and Excretion.** Omeprazole is itself metabolized in the liver, presumably by isozymes of the cytochrome  $P_{450}$ -IIC family.<sup>647, 650</sup> The metabolites are inactive and are excreted mostly in urine, with the remainder being found in stool following biliary excretion.<sup>647</sup> Clearance is not altered in renal failure (Fig. 30-23C).<sup>647, 651</sup>

**Slow Metabolizers: Acquired and Inherited.** Omeprazole clearance is significantly delayed with impaired hepatic function.<sup>647</sup> In elderly subjects clearance is highly variable; therefore, the AUC varies considerably (Fig. 30-23C).<sup>647, 652</sup> It is interesting to note that in a small percentage of normals, hepatic metabolism is also markedly delayed (Figs. 30-23A and 30-23C). This abnormality is reproducible and probably an inherited trait reflecting impaired function of the cytochrome  $P_{450}$ -IIC isozyme that metabolizes omeprazole. In these slow metabolizers, plasma half-life is about three-fold prolonged and the AUC is increased about ten-fold.<sup>652</sup> Drug accumulation does not appear to occur with a daily dosage schedule because the drug is cleared in this period even in slow metabolizers. In light of the wide safety margin with omeprazole, there are no current recommendations to alter dosage in the elderly or in the presence of hepatic failure. However, profound inhibition of acid secretion would be anticipated in slow metabolizers; therefore, these persons are exposed to the theoretical risks of hypochlorhydria (see Consequences of Hypochlorhydria). However, this hypothesis regarding slow metabolizers has not been directly tested. In slow metabolizers who require prolonged omeprazole therapy, cost savings from dosage reductions might justify the effort spent identifying these persons.

**Adverse Effects.** Omeprazole joins the  $H_2$  blockers in having few side effects in short-term use.<sup>653, 654</sup> The absence of side effects may be due in part to the fact that the prodrug is activated only in the acidic compartments of the parietal cell. However, although clinical experience with omeprazole is considerable, the spectrum of rare or delayed untoward effects remains to be fully defined. An elevation of liver enzymes was noted in 30 per cent of patients in one early series, yet numerous other studies have found no evidence of hepatotoxicity,<sup>653, 654</sup> and clinical hepatitis appears rarely.<sup>654a</sup>

**Inhibition of Acid Secretion.** Omeprazole inhibits acid secretion in humans over a dose range from 5 to 80 mg daily; however, the dosage and time dependency of

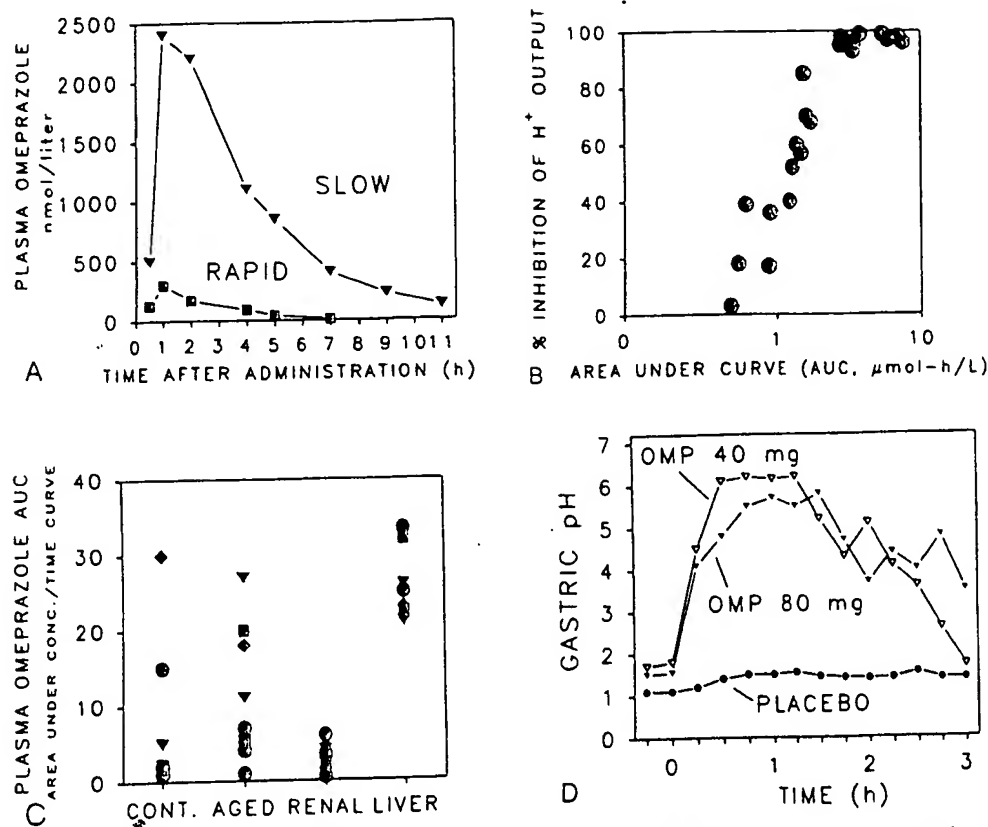


Figure 30-23. Omeprazole pharmacokinetics and pharmacodynamics. A, The plasma concentration curve for rapid and slow metabolizers is shown as a function of time after a 20-mg dose of omeprazole. (Data from Andersson et al.<sup>652</sup>) B, The inhibition of acid secretion by omeprazole is shown as a function of the area under the plasma concentration curve (AUC). (Redrawn from Lind et al. Effect of omeprazole—a gastric proton pump inhibitor—on pentagastrin-stimulated acid secretion in man. Gut 24:270, 1983.) C, The AUC following omeprazole administration is illustrated for control (CONT) and aged subjects and patients with renal or liver failure. (Data from Cederberg et al.<sup>647</sup>) D, Time course for gastric pH following intravenous administration of 40 or 80 mg of omeprazole to fasting subjects. (Data from Baak et al.<sup>651</sup>)

inhibition have several unique features. The effectiveness of antisecretory action increases over the first few days of therapy, probably reflecting progressive increases in bioavailability and inhibition of the  $H^+, K^+$ -ATPase. Furthermore, this lag period is inversely related to dose. A single 10-mg dose has a modest effect on acid secretion, but after five days a 93 per cent reduction in basal secretion and a 66 per cent reduction in pentagastrin-stimulated acid secretion were found.<sup>651</sup> After 7 days of treatment with 10, 20, or 30 mg daily, 24-hour  $H^+$  activity was decreased by 27 per cent, 90 per cent, and 97 per cent, respectively.<sup>655</sup> After a second week of therapy no further increase in inhibition was observed and no further inhibition was found at a dose of 60 mg daily in this group of subjects. The antisecretory action persists for between 24 and 72 hours, reflecting irreversible inhibition of the  $H^+, K^+$ -ATPase.

Although all antisecretory agents produce variable responses, the effectiveness of omeprazole is particularly variable at low, but not high, doses. After seven days on the 10-mg dose, some patients had virtually no inhibition of acid secretion while others experienced >90 per cent inhibition. This variability limits general use of a 10-mg dose.<sup>655, 656</sup> At 20 mg, inhibition is still somewhat variable (Fig. 30-24); however, mean inhibition of acidity ( $H^+$  concentration) is about 90 per cent (Fig. 30-25). At 40

mg, marked inhibition of acid secretion is observed in most subjects (Figs. 30-24 and 30-25). Several hypotheses have been raised to explain this variability (see Hypergastrinemia).

**THE Parietal Cell HAS TO BE TURNED ON TO BE TURNED OFF BY OMEPRAZOLE.** Since omeprazole must be concentrated and activated in the acidic compartments of the parietal cell, omeprazole will inactivate only the  $H^+, K^+$ -ATPase present in actively secreting membrane compartments. In a study of isolated gastric glands *in vitro*<sup>646</sup> or in intact dogs,<sup>657</sup> the effectiveness of omeprazole depended on the degree of activation of acid secretion at the time omeprazole was administered. To underline this point, omeprazole action was markedly compromised if the agent was administered during a time period when acid secretion was inhibited by co-administration of either an  $H_2$  blocker or somatostatin.<sup>657</sup> When given to fasting patients by intravenous bolus, an omeprazole dose of 40 mg every 6 hours produced pH values >4 for 85 per cent of first 24 hours.<sup>658</sup> Two other studies indicated that bolus intravenous doses of 40 mg every 6 hours were necessary to reliably achieve a pH >4.<sup>659, 660</sup> The time course for bolus intravenous omeprazole appears very short when it is administered to fasting subjects. For example, when intravenous omeprazole was given as a single bolus of 40 or 80 mg to subjects at the beginning of an infusion of

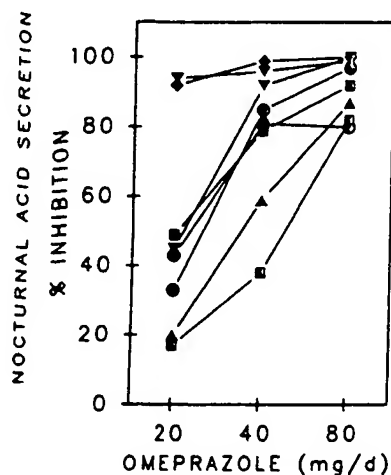


Figure 30-24. Dose response for omeprazole inhibition of nocturnal acid secretion. Acid secretion was determined during four night-time sessions for 7 patients with duodenal ulcer: single doses were given at 8 A.M. of placebo or omeprazole at 20, 40, or 80 mg. Acid secretion was then determined between 9 P.M. and 6 A.M., with the data expressed as a percentage of secretion with placebo. (Data from Shearman et al.<sup>972</sup>)

intravenous amino acids, inhibition of acid secretion by omeprazole lasted for only 3 hours (Fig. 30-23D),<sup>661</sup> rather than the expected 24. These data might suggest that the intravenous route compromised the efficacy of omeprazole. To the contrary, in both humans (C. Cedberg, personal communication) and dogs<sup>657</sup> intravenous omeprazole is fully effective if acid secretion is stimulated by pentagastrin during the omeprazole administration. Furthermore, in gastrinoma patients undergoing surgery, intravenous omeprazole in doses of 60 mg every 12 hours markedly inhibited acid secretion.<sup>662</sup> Intravenous omeprazole also effectively inhibits acid secretion in subjects when administered daily just before breakfast.<sup>662a</sup>

The poor efficacy of omeprazole given by bolus intravenous administration to fasting subjects probably reflects two elements: (1) Administration during a period when the parietal cell is inactive. If the parietal cell is unstimulated when omeprazole is administered, the acidic compartment will be collapsed and the  $H^+$ ,  $K^+$ -ATPase inaccessible to omeprazole because the drug will not be concentrated or activated in the right place. It is important to emphasize that pumps in resting vesicles will be poorly inhibited by omeprazole. With a high proportion of pumps remaining unblocked in the resting cell, the duration of inhibition of omeprazole will be short because the unblocked pumps will be available for recruitment upon subsequent stimulation. (2) With the brief duration of the plasma concentration curve for intravenous administration, inhibition will be limited to those pumps that are activated during this period. Unless parietal cells are stimulated is near maximal, inhibition will be compromised.

**A FEW PRACTICAL POINTS.** The efficacy of omeprazole will depend on whether parietal cells are at rest or activated by food, gastrin, or vagal stimuli during the time the prodrug is circulating. Omeprazole will be most effective when taken with or shortly before meals; effectiveness is likely to be significantly compromised if taken

during a prolonged fasting period. The effectiveness of an evening (9 P.M.) dose is compromised, but only slightly,<sup>662b</sup> presumably because of the postprandial and circadian drive to acid secretion, plus the long duration of action of the enteric-coated preparation.

In the ICU setting with fasting patients, it appears that omeprazole is most effective when given by continuous intravenous administration; however, a dose of about 8 mg/h appears necessary to induce maximal inhibition of acid secretion.<sup>662c</sup> The necessary dosage will probably be markedly reduced if the patient is receiving enteral or possibly parenteral nutrition. There is little clinical experience with these high dosages, and neither these dosages nor the intravenous route is approved by the FDA for use in the United States.

Although not an FDA-approved route of administration for patients with nasogastric or gastrostomy tubes, the omeprazole capsule can be opened and the granules administered via the tube, but these granules should be suspended in an acidic solution (e.g., orange juice) to avoid dissolution if administration or gastric emptying is delayed. However, as noted above, if given during a prolonged fast, effectiveness is likely to be compromised.

Omeprazole should not be co-administered with another antisecretory agent. Higher dosages of omeprazole or more frequent administration rather than combination therapy is indicated if greater antisecretory effectiveness is required.

In most subjects, the 20-mg dosage of omeprazole will not become fully effective until after about four days of therapy. Continuing  $H_2$  blockers during a transition period will be counterproductive. If desired, a "jump start" to omeprazole therapy could be achieved by administering 20 mg of omeprazole every 6 to 8 hours for about 24 hours, although this regimen has not been formally tested. In transition from intravenous  $H_2$  blockers, the relatively

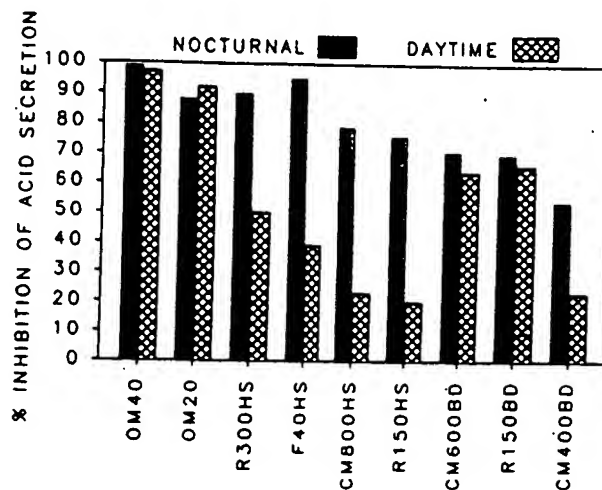


Figure 30-25. The inhibition of gastric acidity by various therapies. Data from 24-hour gastric pH studies were combined from several investigators. The effects on nocturnal and daytime acidity were determined in response to omeprazole 40 mg q.d. (OM40), omeprazole 20 mg q.d. (OM20), ranitidine 300 mg hs (R300HS), famotidine 40 mg hs (F40HS), cimetidine 800 mg hs (CM800HS), ranitidine 150 mg hs (R150HS), cimetidine 600 mg b.i.d. (CM600BD), ranitidine 150 mg b.i.d. (R150BD), and cimetidine 400 mg b.i.d. (CM400BD). (Data from the meta-analysis of Burget et al.<sup>148</sup>)

short half-life of these agents (see Table 30-5) allows omeprazole to be started four to six hours after discontinuation of the  $H_2$  blockers, assuming that the patient is eating.

**NONSELECTIVE AND SELECTIVE ANTIMUSCARINIC AGENTS.** Anticholinergic agents decrease basal and nocturnal gastric acid secretion by about 40 to 50 per cent, and inhibit meal-stimulated gastric acid secretion by about 30 per cent.<sup>663</sup> Their use in acid/peptic disorders has been limited by the well-recognized muscarinic side effects, such as dry mouth, blurred vision, exacerbation of glaucoma, ileus, urinary retention, and tachycardia. *Pirenzepine* is an antimuscarinic antagonist that is semiselective for  $M_1$  receptors, thereby inhibiting acid secretion with a greater relative potency, then interacting with receptors on smooth muscle, heart, and salivary glands.<sup>663, 664</sup> Although structurally related to the tricyclic antidepressants, pirenzepine is hydrophilic and has low permeability across the blood-brain barrier.<sup>665</sup> Presumably because of these properties, at the usual therapeutic dosage (50 mg b.i.d. or t.i.d.) pirenzepine has modest cholinergic side effects (dry mouth, 14 per cent; blurred vision, 2 per cent). Few patients drop out of clinical studies as a result of side effects.<sup>664</sup> *Telenzepine*, another semiselective antimuscarinic agent, is 4 to 20 times more potent than pirenzepine but has a similar overall efficacy and relative specificity for muscarinic receptor subtypes.<sup>666</sup> Although in clinical use in several countries, neither pirenzepine nor telenzepine is approved for use in the United States.

**ANTACIDS.** Antacids containing aluminum and magnesium hydroxide effectively heal ulcers. However, the obvious conclusion that antacids heal ulcers by neutralizing gastric acid may not be correct, in part because there is no correlation between the antacid buffering capacity administered and ulcer healing efficacy (see Acid-independent Duodenal Ulcer Therapy: Antacids Therapy). Furthermore, in animal models, antacids protect gastric mucosa against acute chemical injury in a manner independent of buffering acid<sup>667, 668</sup>; neutralizing the antacid buffering capacity before administration appears to enhance—not reduce—protection against acute mucosal injury in rats. There is a long list of potential mechanisms that may be involved in these acid-independent actions of antacids.<sup>667-669</sup> Several of these mechanisms overlap with those proposed for sucralfate; these agents may share common mechanisms possibly mediated by the aluminum complexes. Antacid and  $Al(OH)_3$  bind EGF and enhance EGF binding to experimental ulcers, thus serving to deliver growth factors to injured mucosa.<sup>668</sup> However, removal of salivary glands, which produce the EGF found in saliva, caused minimal reduction in the healing efficacy of  $Al(OH)_3$  in experimental ulcers, suggesting that growth factors from other sources were bound (for example, transforming growth factor  $\alpha$  is present in gastric juice) or that other mechanisms were involved. Antacids have been shown in preliminary studies to promote angiogenesis in injured mucosa.<sup>210</sup> Antacids also bind bile acids and inhibit pepsin activity.<sup>669</sup> Antacids also influence *H. pylori* status; heavy metals are well known to suppress—but generally not eradicate—*H. pylori*. It is not yet known which of these actions observed in animal models translate into promoting ulcer healing in human peptic ulcer disease, but antacids appear to do more than buffer acid.

**Adverse Effects.** Antacids have side effects that are a function of the quantity consumed and the duration of therapy. Magnesium-containing antacids cause diarrhea, and hypermagnesemia, the latter only being a significant problem in the face of renal failure. Antacids may also contain considerable sodium, and sodium overload can occur in susceptible patients. Ingestion of large amounts of calcium and absorbable alkali, particularly calcium carbonate, can lead to hypercalcemia, alkalosis, and renal impairment, the venerable milk-alkali syndrome.<sup>670, 671</sup> Calcium-containing antacids, but not Al/Mg antacids, also stimulate acid and gastrin secretion,<sup>672</sup> thereby inducing "acid rebound."<sup>673</sup> Aluminum absorption and effects on mineral metabolism are discussed subsequently.

**SUCRALFATE.** *Sucralfate* (Carafate) is a sulfated polysaccharide, sucrose octasulfate, complexed with aluminum hydroxide. Sucralfate prevents acute, chemically induced mucosal damage and heals chronic ulcers without altering gastric acid or pepsin secretion or significantly buffering acid.<sup>674, 675</sup> The several mechanisms proposed for the antiulcer actions of sucralfate parallel those described for antacids, probably because of the shared  $Al(OH)_3$  content.<sup>674, 675</sup> Sucralfate inhibits peptic activity by impairing the pepsin-substrate interaction, and it binds bile salts and increases mucosal prostaglandin production.<sup>209, 674-676</sup> In preliminary studies, sucralfate has been found to stimulate angiogenesis and formation of granulation tissue in an *in vivo* wound healing model.<sup>209</sup> These actions are shared with various growth factors, such as fibroblast growth factor (FGF), and sucralfate binds FGF with high affinity.<sup>209</sup> In turn, sucralfate binds to the ulcer base and thus is positioned to deliver growth factors to the wound. By coating the ulcer bed, sucralfate could also potentially reduce the access of pepsin and acid. Although  $Al(OH)_3$  appears to mediate some of these actions, the sucrose octasulfate moiety may also play a role, possibly by contributing sulfhydryl groups to reduce oxidant damage to epithelial cells. The binding of this agent to the ulcer base is enhanced at a pH below 3.5, leading to the recommendation that the drug be administered 30 to 60 minutes before meals. It is not clear which of these actions underlie mucosal protection against acute injury and which ones underlie the healing actions on chronic peptic ulcers.

**Adverse Effects.** Sucralfate has minimal untoward effects, and in short-term drug trials side effects are not clearly different from those of placebo.<sup>676</sup> Sucralfate can bind other drugs (see Table 30-6) if taken simultaneously, although the clinical consequences are minor.

**ALUMINUM AND MINERAL METABOLISM WITH SUCRALFATE AND ANTACIDS.** Absorption of aluminum occurs from several antacid formulations.<sup>677</sup> Daily consumption of doses as low as 120 mmol of antacid tablets increases serum and urinary aluminum levels during four weeks of therapy.<sup>678</sup> A therapeutic dose of sucralfate contains about 0.8 gm of aluminum and the absorption of aluminum is comparable to that seen with aluminum hydroxide antacids, representing about 0.005 per cent of the ingested amount.<sup>679</sup> During therapy with 4 gm sucralfate daily, serum and urine aluminum levels crease. Aluminum is generally readily excreted by normal kidneys, and urinary levels remain elevated for one to three weeks after discontinuing therapy.<sup>679-681</sup> Thus, with



normal renal function, any body burden of aluminum appears to be eliminated within a few weeks after therapy stopped. However, significant retention can occur with renal failure; neurotoxicity and brain deposition of aluminum can develop in this setting with antacids<sup>676</sup> or sucralfate.<sup>676, 680</sup>

Even in subjects with normal renal function, simultaneous consumption of citric acid enhances absorption of aluminum from antacids by 50-fold, resulting in considerable elevations in serum aluminum concentration.<sup>678, 683</sup> It is likely that citric acid produces similar enhancement of aluminum absorption from sucralfate. To avoid enhanced aluminum absorption, especially in the setting of renal failure, it is advisable to avoid combining antacids or probably sucralfate with foods or other agents that contain citric acid (e.g., Alka-Seltzer).<sup>684</sup>

The extent and consequences of aluminum deposition in tissues with sustained use of either class of agents have not been defined, but the possibility of significant aluminum retention in the face of normal renal function is remote. In rats following eight weeks of sucralfate treatment approximating therapeutic dosages in humans, some difference in bone concentrations of aluminum was noted.<sup>685</sup> Although aluminum deposits have been reported in brain tissue in Alzheimer's disease, evidence argues against significant aluminum deposition in brain or a role for this metal in pathogenesis.<sup>684, 686, 687</sup> However, more rigorous investigation of tissue aluminum is required in humans before firm conclusions can be reached.

Aluminum salts block intestinal absorption of dietary phosphate; in two weeks of therapy with moderate doses, significant hypophosphatemia can develop, especially if the patient is on a low-phosphate diet or is phosphate-depleted for other reasons.<sup>688</sup> Sucralfate also binds phosphate, leading to similar theoretical consequences, and combining sucralfate and antacids can potentially amplify these effects.<sup>681</sup> With prolonged phosphate depletion, mineral metabolism is disrupted, urinary and fecal excretion of calcium are increased, and osteoporosis, osteomalacia, and pathologic bone fractures can develop.<sup>681, 689</sup> Although the untoward consequences of prolonged full-dose sucralfate or antacid therapy are likely to be quite small, some caution is required until further studies are available. Both sucralfate and antacids warrant cautious use in patients with renal failure.

**BISMUTH.** The venerable status of bismuth as therapy for dyspepsia has been adorned with numerous hypotheses regarding mechanisms, the most recent of which is the suppression of *H. pylori*. Two forms of bismuth are most commonly used: colloidal bismuth subcitrate (CBS), also known as tripotassium dicitrate bismuthate (DeNol), and bismuth subsalicylate (BSS, Pepto-Bismol). Neither is approved for therapy of peptic ulcer in the United States. BSS is an insoluble complex, with 30 ml containing 258 gm of salicylate and 303 mg of bismuth.<sup>690</sup> At a pH <3.5, HCl reacts with the complex, forming bismuth oxychloride and liberating salicylate, which is readily absorbed. CBS is a complex bismuth salt that also forms bismuth oxychloride as the complex dissolves in HCl. An elevated gastric pH may interfere with activation of bismuth compounds in the stomach. In the colon, with both agents bismuth salts react with hydrogen sulfide to form bismuth sulfide, which blackens the stools.<sup>690</sup> Pre-

sumably the free  $\text{Bi}^{3+}$  is responsible for the biologic actions.

**Proposed Mechanisms of Ulcer Healing.** Bismuth does not inhibit or neutralize gastric acid secretion. However, pepsin activity was significantly inhibited and mucous secretion appeared enhanced by four weeks of treatment with CBS.<sup>691</sup> CBS decreases pepsin degradation of mucus and EGF,<sup>692</sup> a finding that may explain the apparent inhibition of pepsin output. As with  $\text{Al}(\text{OH})_3$  and sucralfate, bismuth from CBS may bind to the ulcer bed.<sup>693, 694</sup> An abundance of macrophages surrounded the ulcer base in CBS-treated rats but not in the control group<sup>693</sup>; recruitment of macrophages could promote healing. CBS may also increase mucosal prostaglandin production<sup>695</sup> and mucosal bicarbonate secretion. Bismuth has not yet been reported to stimulate angiogenesis or to bind growth factors, but this parallel with the other heavy metals of ulcer therapy would not be surprising. Interestingly, BSS may not share the antiulcer properties of CBS, although data are limited.<sup>690, 696</sup> Heavy metals frequently exhibit antimicrobial activity, and the most dramatic action of bismuth, including both BSS and CBS, is the suppression of *H. pylori*,<sup>52, 690</sup> as considered subsequently (see *Helicobacter pylori* and Ulcer Therapy). The contributions to ulcer healing from these various effects of bismuth remain to be sorted out. A comparison of the effects of bismuth and combinations of antibiotics that also eradicate *H. pylori* in the absence of bismuth may help elucidate the antibacterial versus direct ulcer-healing properties of bismuth.

**Adverse Effects.** The primary concern with bismuth compounds is bismuth absorption resulting in bismuth intoxication, which was a clinical problem particularly when bismuth subgallate was used for prolonged periods at high dose. Bismuth absorption varies with the specific form of bismuth; absorption is much greater with CBS than with BSS or bismuth subnitrate.<sup>697-699</sup> Furthermore, co-administration of  $\text{H}_2$  blockers increases bismuth absorption from CBS but apparently not from BSS or bismuth subnitrate.<sup>696a</sup> At the end of six weeks of therapeutic doses of CBS, serum bismuth concentrations are elevated.<sup>690, 700</sup> An occasional patient will have serum bismuth levels approaching the pretoxic range of 50 ng/ml.<sup>700</sup> However, a recent study indicated that following a single dose of CBS, peak plasma concentrations of 100 ng/ml were reached in 9 of 16 subjects.<sup>699</sup> Despite these surprising transient increases in plasma bismuth concentrations, significant toxicity has not been reported in clinical trials or with intermittent use of CBS or BSS.<sup>690, 700</sup> A body burden of bismuth does accumulate, and urine bismuth levels are somewhat elevated for up to three months after termination of an ulcer treatment regimen.<sup>701</sup> In light of the absorption of bismuth from CBS, this agent is indicated only for intermittent therapy. Further studies are indicated with BSS and bismuth subnitrate. Since renal failure interferes with bismuth excretion, bismuth should be avoided or, if patients with renal failure are treated with bismuth, serum bismuth levels monitored.

**PROSTAGLANDINS.** Prostaglandins, particularly of the E and I group, inhibit acid secretion by selectively reducing the ability of the parietal cell to generate cyclic AMP in response to histamine. Prostaglandin receptors act via

an inhibitory GTP (guanosine triphosphate)-binding protein of adenylate cyclase to produce this effect.<sup>242</sup> Prostaglandins also enhance mucosal defense mechanisms (see Pathophysiology of NSAID Ulcers). When these two actions were recognized, enthusiasm was generated over the possibility that therapy with prostaglandins would dramatically heal and prevent ordinary peptic ulcers, an effect that has not materialized (see Secretory Inhibition and Duodenal Ulcer Healing: Prostaglandins). Naturally occurring prostaglandins are unstable, being metabolized primarily by oxidation at the 15 position on the eight-carbon side chain.<sup>701a</sup> Therefore, analogs were synthesized with modified structure on this side chain to provide resistance to degradation.

Misoprostol (Cytotec) is a 15-deoxy-15-hydroxy-16-methyl analog of prostaglandin E<sub>1</sub>. Misoprostol shares the properties of other E analog type prostaglandins, displaying moderate inhibition of basal and food-stimulated acid secretion in humans.<sup>702, 703</sup> Enprostil is a 15-dehydro analog of PGE<sub>2</sub> with a higher potency and duration of antiseecretory action.<sup>704, 705</sup> Topical action appears crucial in prostaglandin action; oral administration gives greater antiseecretory efficacy and fewer side effects than does systemic administration.<sup>705</sup> In addition to inhibiting acid secretion, these E-type prostanoids enhance mucosal resistance to injury in animal models.<sup>702, 705</sup> Although structurally related, there are subtle differences in the actions of these prostanoids on gastric function, such as the ability of high concentrations of PGE<sub>2</sub> and misoprostol, but not enprostil, to stimulate adenylate cyclase.<sup>706</sup> These differences suggest the possibility that these prostaglandins will have actions that differ from endogenous prostanoids. The prostanoids that have undergone clinical study for peptic diseases include misoprostol, enprostil, rioprostil, and arbaprostil; only misoprostol has been approved for use in the United States for prevention of NSAID-induced gastric ulcer.

**Adverse Effects.** The most frequent side effects of the E type prostanoids are crampy abdominal pain and diarrhea, which are dose-dependent effects.<sup>239, 707</sup> Diarrhea occurred in 3 to 39 per cent of patients on the 200 µg q.i.d. dose of misoprostol, with the range reflecting the definition and the mode of data collecting.<sup>239, 707</sup> It has been hypothesized that subjects consuming NSAIDs have an increased sensitivity to the diarrhegenic effect. Diarrhea is often mild and transient, and may respond to a temporary reduction in dose. In clinical trials usually less than 5 per cent of the subjects drop out because of diarrhea. However, in clinical practice these side effects interfere with compliance in a larger portion of patients. The diarrhea is less with the 100-µg q.i.d. dose and initiating therapy with this lower dose will reduce problems with diarrhea. Administration with meals and avoidance of magnesium antacids also reduce diarrhea.

Prostaglandins of the E group are generally uterotropic; misoprostol (400 µg) was given to 35 pregnant women the night before they were to undergo elective abortion; this dose induced bleeding or cramps in 10 per cent of these women.<sup>707</sup> Misoprostol is clearly contraindicated in women of childbearing potential not on contraception. All patients should be informed of this risk, to minimize the possibility that the drug could be inadvertently given by the patient to a pregnant woman.

**OTHER MODALITIES.** Two other modalities that have some efficacy in treatment of peptic disease will be considered only briefly because side effects preclude use in the era when numerous safe therapies are available. The tricyclic antidepressants *doxepin* and *trimipramine* have some efficacy healing duodenal ulcers.<sup>708</sup> It is unknown whether these agents have actions other than modest inhibition of acid secretion, which probably reflects interaction at histamine H<sub>2</sub> and/or cholinergic receptors. These agents cause cardiac arrhythmias and several other side effects.

*Carbenoxolone*, a licorice extract, also has efficacy in healing peptic ulcers<sup>709-711</sup> but causes fluid retention, congestive heart failure, hypokalemia, and hypertension. Despite numerous theories and a few studies, the mechanism of action remains unknown; this agent does not alter gastric acid or pepsin secretion.

### DRUG INTERACTIONS

**Absorption.** As a result of intraluminal binding, antacids and sucralfate decrease absorption of a number of drugs (see Table 30-6).<sup>712, 713</sup> It is best to advise separation of consumption of antacids and other drugs by an hour. Bismuth may have the same effect; studies are limited.<sup>700</sup> Antiseecretory agents, by increasing intraluminal pH, can alter absorption. The effect of antiseecretory agents on absorption of vitamin B<sub>12</sub> can be quite dramatic.<sup>714, 715</sup> The effect appears to be mediated by the increase in pH rather than inhibition of intrinsic factor secretion.<sup>602</sup> The absorption of iron and calcium can also be compromised. These effects are more evident with sustained inhibition of acid secretion rather than with inhibition of only nocturnal secretion. Altered B<sub>12</sub>, iron, or calcium absorption would become an important consideration only if marked acid inhibition were sustained for a prolonged period of time.

Dissolution of some drugs, particularly weak bases, is decreased with gastric neutralization. The consequences depend on the specific drug and its preparation; for example, decreased dissolution of ketoconazole, a weak base, significantly decreases absorption.<sup>696a</sup> Alternatively, the absorption of bismuth from CBS is increased, presumably because decreased gastric acidity increases free bismuth concentrations.<sup>532</sup> Once a drug is solubilized in gastric juice, the absorption of drugs that are weak acids from the stomach may be decreased, whereas absorption of weak bases may be increased. However, gastric absorption is usually modest compared with intestinal absorption. A beneficial drug interaction occurs when acid secretory inhibitors decrease the absorption of weak acids such as aspirin, thereby reducing concentration within and damage to the gastric mucosa.

**Drug Interactions via Cytochrome P<sub>450</sub>.** Cimetidine, omeprazole, and to a lesser extent ranitidine inhibit members of the cytochrome P<sub>450</sub> superfamily of mixed function oxidases, thereby interfering with certain compounds metabolized by these (phase I) reactions. Several features of P<sub>450</sub> metabolism are important with respect to the antiulcer drugs<sup>602</sup>: (1) The effects are time-dependent, and generally three to five days are needed to reach maximal inhibition of drug metabolism. (2) The effects are dependent on dose of drug and the time of the dosing. For example, a night-time dose of cimetidine has less effect on metabolism of R-warfarin than does a split-dose

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[54] METHODS AND PHARMACEUTICAL  
COMPOSITIONS FOR TREATING  
EPISODIC HEARTBURN

[75] Inventor: M. Michael Wolfe, Newton, Mass.  
[73] Assignee: Brigham and Women's Hospital, Inc.,  
Boston, Mass.

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424/692; 424/717; 514/63; 514/365; 514/370;  
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[58] Field of Search ..... 424/688, 687, 682, 690,  
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819

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Primary Examiner—Frederick E. Waddell

Assistant Examiner—Raymond J. Henley, III

Attorney, Agent, or Firm—Ruden, Barnett, McClosky,  
Smith, Schuster & Russell

[57] ABSTRACT

Pharmaceutical medications and methods are disclosed  
for providing instant and sustained relief from pain or  
symptoms associated with episodic heartburn in hu-  
mans. The medications consist essentially of antacids  
and histamine H<sub>2</sub>-receptor antagonists, and may be  
administered on an as-needed basis in liquid or solid  
dosage forms. Typical antacids which may be used in  
combination with the histamine H<sub>2</sub>-receptor antagonist  
are conventional antacids which are well known and  
widely used in the treatment of excess acid related gas-  
trointestinal dysfunctions. Exemplary of typical anti-  
acids include, sodium bicarbonate, calcium carbonate,  
magnesium hydroxide and aluminum hydroxide, as well  
as commercially available high potency, flavored anti-  
acids. Histamine H<sub>2</sub>-receptor antagonists which may be  
used in combination include those conventionally used  
in the treatment of peptic ulcers, such as, for example,  
cimetidine, ranitidine, famotidine and nizatidine. In  
carrying out the methods, an antacid and histamine  
H<sub>2</sub>-receptor antagonist may be administered together as  
a single unitary dose in the form of a liquid or solid, or  
administered together, but separately as either liquids or  
solids or a combination thereof. The oral medications  
when formulated as a single unitary dose may include  
other additives, such as, for example, antifoamants,  
flavorings, sweeteners and the like.

27 Claims, No Drawings



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# METHODS AND PHARMACEUTICAL COMPOSITIONS FOR TREATING EPISODIC HEARTBURN

## FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions and methods for providing immediate and sustained relief from pain, discomfort and/or symptoms associated with episodic heartburn in humans.

## BACKGROUND

About 7-10 percent of all people suffer daily, and about 25-40 percent monthly, from pain, discomfort and/or symptoms associated with episodic heartburn. Episodic heartburn is defined as the sensation of burning under the sternum (breastbone) and is usually associated with the ingestion of different foods. Episodic heartburn has also been referred to as "sour stomach," "indigestion," and "waterbrash/regurgitation." Although different foods, such as coffee, mints, fatty foods, alcohol, and chocolate, are usually implicated in the etiology of episodic heartburn, these symptoms can be caused by any type of food in certain people. Moreover, in many people, there is no inciting agent that can be identified, rather the disorder occurs without any known provocation.

At present, the primary treatment is based upon the neutralization of gastric acid and pepsin with antacids, such as, for example, aluminum hydroxides, calcium carbonates, magnesium hydroxides and sodium bicarbonates. Of less importance, treatment is based upon the inhibition of secretion by histamine H<sub>2</sub>-receptor antagonists, such as cimetidine and ranitidine.

Unfortunately, both of these treatments have proven to be inadequate. The problem with antacids is that they provide only transient relief. This disadvantage is emphasized in many people at night where symptomatic relief is not provided. The problem with histamine H<sub>2</sub>-receptor antagonists is that relief is typically not experienced until about forty minutes to about two hours after the medication is ingested. Moreover, the simultaneous administration of antacids and histamine H<sub>2</sub>-receptor antagonists have been discouraged based upon studies demonstrating that antacids decrease absorption and subsequent blood levels of histamine H<sub>2</sub>-receptor antagonists, such as cimetidine and ranitidine. See, for example, Steinberg, W. et al.: *N. Engl. J. Med.*, 307:400-404 (1982), and Frislid, K. et al.: *Br. Med. J.*, 286:1358 (1983); and Mihaly, G. W. et al.: *Br. Med. J.*, 285(6347):998-9 (Oct. 9, 1982).

Consequently, there is a need for a treatment which can effectively provide both instant and sustained relief from pain, discomfort and/or symptoms associated with episodic heartburn in humans.

## SUMMARY OF THE INVENTION

In brief, the present invention alleviates and overcomes certain of the above-mentioned drawbacks and shortcomings through the discovery of novel pharmaceutical compositions and methods for providing immediate, temporary and sustained relief to people who suffer from episodic heartburn. Generally speaking, the pharmaceutical compositions include an effective amount of an antacid and a histamine H<sub>2</sub>-receptor antagonist, and the methods involve administering together or substantially together an antacid and a histamine H<sub>2</sub>-receptor antagonist at or after the onset of

pain, discomfort and/or symptoms caused by episodic heartburn. The present invention is based upon the unexpected realization that antacids and histamine H<sub>2</sub>-receptor antagonists can be effectively administered together or substantially together to achieve continuous relief from pain, discomfort and/or symptoms associated with episodic heartburn, notwithstanding current medical teachings against the simultaneous administration of antacids and histamine H<sub>2</sub>-receptor antagonists.

The novel pharmaceutical compositions of the instant invention are formulated so that they can be administered orally on an as needed basis to obtain the symptomatic relief. In other words, it is not necessary to take the novel pharmaceutical compositions or practice the methods of the present invention on a regimented schedule to obtain effective relief. Rather, the compositions can be taken and the methods of the present invention can be practiced by people whenever needed, that is, at the onset of pain, discomfort or symptoms, or whenever pain, discomfort or symptoms are experienced. In accordance with the present invention, this is simply accomplished by orally ingesting together or at basically the same time, an effective amount of an antacid and an H<sub>2</sub>-receptor antagonist whenever an attack of episodic heartburn has surfaced.

The above features and advantages of the present invention will be better understood with reference to the following Detailed Description and Examples which are illustrative of the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

By way of illustrating and providing a more complete appreciation of the present invention and many of the attendant advantages thereof, the following Detailed Description is given concerning the novel pharmaceutical compositions and methods for providing people suffering from episodic heartburn with instant and sustained relief.

As set forth in the Background, by the term "episodic heartburn," it is meant herein to refer to the sensation of burning under the sternum (breastbone) usually, but not necessarily, associated with the ingestion of different foods. Also included in this definition of "episodic heartburn" is sour stomach, indigestion and waterbrash/regurgitation.

By the term "histamine H<sub>2</sub>-receptor antagonist(s)," it is referred to herein in a broad sense and is meant to include those agents that inhibit or block the secretion of gastric acid by binding to a specific histamine receptor on the parietal (acid-secreting) cell membrane located in the stomach. Exemplary of histamine H<sub>2</sub>-receptor antagonists contemplated by the present invention are cimetidine, ranitidine, nizatidine and famotidine.

By the term "antacid(s)," it too is used broadly herein and refers to those agents which can block gastric acid and/or bile salts by neutralization, and/or inhibit the proteolytic activity of pepsin. Antacids which may be used in combination with the histamine H<sub>2</sub>-receptor antagonists in the present invention are conventional antacids which are well known and widely used in the treatment of a variety of excess acid-related gastrointestinal dysfunctions including acid indigestion, heartburn, sour stomach and ulcers. Typical antacids contemplated by the present invention include, for example, aluminum hydroxides, calcium carbonates, magnesium hydroxides, sodium bicarbonates and the like, as

well as those antacids that are commercially available. In accordance with the present inventions, the antacids may be used in dosage amounts conventionally used for treatment of a variety of excess acid-related gastrointestinal dysfunctions, as discussed above.

By the terms "immediate, temporary and sustained relief," they too are used in a broad sense herein. More particularly, the term "immediate relief" means that relief obtained from pain, discomfort and/or symptoms associated with episodic heartburn which occurs within about 5-10 minutes following ingestion of the active ingredients or an antacid. "Temporary relief" on the other hand refers to relief from pain, discomfort and/or symptoms associated with episodic heartburn which lasts in duration on the order of between about 30 minutes and 90 minutes after ingestion of the active ingredients or an antacid. With respect to "sustained relief," it refers to relief obtained from pain, discomfort and/or symptoms associated with episodic heartburn which lasts in duration for over about 4-6 hours following ingestion of the active ingredients or the histamine H<sub>2</sub>-receptor antagonists. It should therefore be appreciated that by the term "immediate and sustained relief," it means herein immediate, temporary and sustained relief which starts within about 5-10 minutes following ingestion of the active ingredients and continues and remains constant for at least about 4-6 hours after ingestion of the active ingredients; the actual ingredients being an antacid and a histamine H<sub>2</sub>-receptor antagonist.

The pharmaceutical medications of the instant invention can be conveniently prepared from, for example, commercially available antacids and histamine H<sub>2</sub>-receptor antagonists and may be formulated into liquid or solid dosage forms or combinations thereof. For example, the pharmaceutical medications may be taken as a single unitary dose containing both the antacid and the histamine H<sub>2</sub>-receptor antagonist in a liquid or solid dosage form. Likewise, the present invention contemplates taking the ingredients substantially together, but separately in the same or different dosage forms, such as taking the antacid as a liquid dose and the histamine H<sub>2</sub>-receptor antagonist as a solid dose or vice versa, or taking them both separately as either solid or liquid doses.

When taking the active ingredients substantially together, but separately in same or different dosage forms, the order in which they are ingested is not critical. In other words, the antacid and the histamine H<sub>2</sub>-receptor antagonist may be ingested simultaneously, or the antacid may be ingested first followed by the histamine H<sub>2</sub>-receptor antagonist, or the H<sub>2</sub>-receptor antagonist may be first ingested followed by the antacid. It is preferable, however, to formulate the antacids and the histamine H<sub>2</sub>-receptor antagonists into single liquid mixtures which can be co-ingested as single unitary dosages on an as-needed basis, i.e., at or after the onset of pain, discomfort and/or symptoms associated with episodic heartburn. When commercially available antacids are selected for use in accordance with the present invention, such as Maalox-Plus®, Mylanta®, Tums®, Gelusil®, etc., it is preferable to use the high potency, flavored (mint, cherry, lemon, etc.) liquid antacids, such as, for example, Maalox-Plus® and Mylanta-II®.

By the term "substantially together," it is meant herein that when the active ingredients, i.e., an antacid and a histamine H<sub>2</sub>-receptor antagonist, are taken in separate dosage forms, they can be consumed either simultaneously or within a period of time such that the

immediate, temporary and sustained relief obtained is constant and uninterrupted. For example, the active ingredients may be taken together or within a few seconds to a few minutes of one another. Nevertheless, it is preferable to ingest a single unitary dose which includes both active ingredients and is in liquid form.

Typical dosages include about 30 mls or 2 tablespoons of a high-potency antacid having an acid-neutralizing capacity equal to the present formulations of, for example, Maalox Plus®, Mylanta-II®. With respect to the histamine H<sub>2</sub>-receptor antagonist, the amount included in the single dosages is believed to be about 200 mg to about 300 mg of cimetidine or about 100 mg to about 150 mg of ranitidine. For example, a typical dosage amount for providing immediate and sustained relief from episodic heartburn in an adult is about 30 mls of a high potency flavored antacid or the equivalent thereof and about 200 mg to about 300 mg of cimetidine or 100 mg to about 150 mg of ranitidine administered between about one and about four times per day. Notwithstanding, it should be appreciated that the oral medications of the instant invention are to be taken on an as-needed basis whenever pain or symptoms associated with episodic heartburn is experienced.

Antiflatulents may also be used in combination with the antacids and histamine H<sub>2</sub>-receptor antagonists in the present invention and include those antiflatulents which are conventionally used in the treatment of gastrointestinal dysfunction, such as, for example, simethicone. Antiflatulents may be used in the present invention in dosage amounts conventionally used in the treatment of gastrointestinal dysfunction.

The pharmaceutical compositions may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacturer of pharmaceutical compositions and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and the like, in order to provide a pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. These excipients may be, inert diluents, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example, starch, gelatine or acacia, and lubricating agents, for example, magnesium stearate or stearic acid. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide an even longer sustained action over a period of time.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with a suitable oil medium, for example, arachis oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active ingredients in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients may be suitable suspending agents, for example, sodium carboxymethyl

cellulose, methyl cellulose, hydroxy propyl methyl cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be any suitable naturally occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example, polyoxyethylene sorbitol monnoleate, or condensation product of ethylene oxide with partial esters derived from fatty acids and hexitol and anhydrides, for example, polyoxyethylene sobirtan monnoleate. The aqueous suspensions may also contain one or more suitable preservatives, for example, ethyl, or n-propyl, p-hydroxy benzoate, one or more suitable coloring agents, one or more suitable flavoring agents and one or more suitable sweetening agents, such as sucrose, saccharin, or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and on or more preservatives. Suitable dispersing or wetting agents and suspending agents may be exemplified by those already mentioned above. Additional suitable excipients, for example, sweetening, flavoring and coloring agents, may also be present.

Syrups and elixirs may be formulated with suitable sweetening agents, for example, glycerol, sorbitol, or sucrose. Such formulations may also contain suitable demulcents, preservatives and flavoring and coloring agents.

In order to further illustrate the present invention and the advantages thereof, the following specific Examples are given, it being understood that these Examples are intended only to be illustrations without serving as a limitation on the scope of the present invention.

#### EXAMPLE I

A 49-year old man diagnosed with episodic heartburn relating to dietary indiscretion was treated with a histamine H<sub>2</sub>-receptor antagonist. He reported that, while the histamine H<sub>2</sub>-receptor antagonist produced symptom relief, he did not experience relief until some time after he ingested the medication.

This man was then treated with 400 mg of cimetidine (tablet), 30 mls of Maalox Plus® (liquid), or both. He reported that the Maalox-Plus® produced symptomatic relief, but that a second dose was necessary after one-half hour. He also reported that the cimetidine relieved the heartburn, but only after about 45 to 60 minutes. He reported, however, that the combination of both Maalox-Plus® and cimetidine produced immediate (within 5 minutes) as well as temporary and sustained relief. He further reported that there was no decrease in the length of time in which relief was obtained when both were taken together.

#### EXAMPLE II

A 41-year old man diagnosed with episodic heartburn relating to dietary indiscretion was treated with 30 mls of Maalox-Plus® (liquid), 300 mg of cimetidine (liquid), or both. He reported that symptom relief was superior with the combination, when compared to using each individual agent alone. More particularly, he re-

ported that when the Maalox-Plus® was used alone, he obtained immediate, but only temporary, relief, and that when cimetidine was used alone, he reported relief of heartburn after 45-60 minutes. However, when he used them together, he reported immediate, temporary and sustained relief from heartburn following ingestion.

#### EXAMPLE III

A 33-year old man diagnosed with episodic heartburn relating to dietary indiscretion was treated with 30 mls of Maalox Plus® (liquid), 150 mg of ranitidine (tablet), or both. He reported that symptom relief was superior with a combination, when compared to using each individual agent alone. More particularly, he reported that when the Maalox-Plus® was used alone, he obtained only partial relief within about 10 minutes after ingestion, which lasted only about 30 minutes, and that when ranitidine was used alone, he reported complete relief that began approximately about 60 minutes after ingestion and lasted about 8 hours. However, when he used them in combination, he reported partial relief within about 10 minutes, but complete relief within about 45 minutes, lasting about 8 hours after ingestion.

#### EXAMPLE IV

A 21-year old man diagnosed with episodic heartburn relating to dietary indiscretion was treated with Tums® tablets, 150 mg of ranitidine (tablet), or both. He reported that symptom relief was superior with a combination, when compared to using each individual agent alone. More particularly, he reported that when the Tums® were used alone, he obtained relief within about five minutes after ingestion, for about one hour, and that when ranitidine was used alone, he reported complete relief after 45 minutes, which lasted indefinitely. However, when he used them in combination, he reported immediate, temporary and sustained relief following ingestion.

#### EXAMPLE V

A 31-year old man diagnosed with episodic heartburn relating to dietary indiscretion was treated with 30 mls of Mylanta II® (liquid), 400 mg of cimetidine (tablet), or both. He reported that symptom relief was superior with a combination, when compared to using each individual agent alone. More particularly, he reported that when the Mylanta II® was used alone, he had relief of heartburn within 3-5 minutes after ingestion, and that when cimetidine was used alone, he reported complete and sustained relief after 30-40 minutes following ingestion. However, when he used them in combination, he reported immediate, temporary and sustained relief following ingestion.

#### EXAMPLE VI

A 50-year old woman diagnosed with episodic heartburn relating to dietary indiscretion was treated with 30 mls of Maalox Plus® (liquid), 400 mg of cimetidine (tablet), or both. She reported that symptom relief was superior with a combination, when compared to using each individual agent alone. More particularly, she reported that when the Maalox-Plus® was used alone, she obtained only partial immediate relief lasting 60 minutes, and that when cimetidine was used alone, she reported complete and sustained relief within 30-40 minutes. However, when he used them in combination, she reported partial relief within 5-10 minutes and com-

plete sustained relief within 30 minutes following ingestion.

#### EXAMPLE VII

A 32-year old man with alleged episodic heartburn related to dietary indiscretion was treated with 30 mls of Mylanta II® (liquid), 400 mg of cimetidine (tablet), or both. He reported no relief of symptoms with any of the regimens examined. Upon further questioning of the man and diagnosis, it was determined that his symptoms were actually associated with abdominal bloating and flatulence, not episodic heartburn.

The present invention may, of course, be carried out in other specific ways than those herein set forth without departing from the spirit and essential characteristics of the invention. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive and any changes coming within the meaning and equivalency range of the appended claims are to be embraced therein.

Having described my invention, I claim:

1. A method of providing immediate and sustained relief from pain, discomfort and/or symptoms associated with episodic heartburn in a human, said method comprising:

orally administering to a human together or substantially together an antacid in an amount effective to substantially neutralize gastric acid and a histamine H<sub>2</sub>-receptor antagonist in an amount effective to substantially inhibit or block gastric acid secretion for providing the human with immediate and sustained relief from pain, discomfort and/or symptoms associated with episodic heartburn, the immediate and sustained relief provided lasting longer in duration than when the human is orally treated with only the antacid and the immediate and sustained relief provided being faster than and lasting at least about as long in duration as when the human is orally treated with only the histamine H<sub>2</sub>-receptor antagonist.

2. A method of claim 1, the histamine H<sub>2</sub>-receptor antagonist being cimetidine.

3. A method of claim 1, the histamine H<sub>2</sub>-receptor antagonist being ranitidine.

4. A method of claim 1, the histamine H<sub>2</sub>-receptor antagonist being selected from a group consisting of famotidine and nizatidine.

5. A method of claim 1, the antacid being selected from a group consisting of aluminum hydroxide, calcium carbonate, magnesium hydroxide, sodium bicarbonate and mixtures thereof.

6. A method of claim 1, the antacid being a high potency antacid.

7. A method of claim 1, the antacid being a flavored antacid.

8. A method of claim 2, the cimetidine being administered in a daily dosage amount of between about 200 mg and about 1200 mg.

9. A method of claim 3, the ranitidine being administered in a daily dosage amount of between about 100 mg and about 450 mg.

10. A method of claim 1, said method including the further step of administering an effective gas inhibiting amount of an antifatulent.

11. A method of claim 10, the antifatulent being simethicone.

12. A method of claim 1, the antacid and the histamine H<sub>2</sub>-receptor antagonist being administered in a dosage form selected from a group consisting of liquid and solid dosage forms and mixtures thereof.

13. An oral pharmaceutical medication for providing immediate and sustained relief from pain, discomfort and/or symptoms associated with episodic heartburn in a human, said oral pharmaceutical medication consisting essentially of:

an antacid in an amount effective to substantially neutralize gastric acid;

a histamine H<sub>2</sub>-receptor antagonist in an amount effective to substantially inhibit or block gastric acid secretion; and

a pharmaceutically acceptable carrier;

said oral pharmaceutical medication providing immediate and sustained relief from pain, discomfort and/or symptoms associated with episodic heartburn in the human, said immediate and sustained relief lasting longer in duration than when the human is orally treated with only the antacid and being faster than and lasting at least about as long in duration as when the human is orally treated with only the histamine H<sub>2</sub>-receptor antagonist.

14. A pharmaceutical medication of claim 13, said oral pharmaceutical medication being in a liquid dosage form.

15. A pharmaceutical medication of claim 13, said oral pharmaceutical medication being in a solid dosage form.

16. A pharmaceutical medication of claim 13, said histamine H<sub>2</sub>-receptor antagonist being cimetidine.

17. A pharmaceutical medication of claim 16, said cimetidine being present in an amount of between about 200 mg and about 300 mg.

18. A pharmaceutical medication of claim 13, said histamine H<sub>2</sub>-receptor antagonist being ranitidine.

19. A pharmaceutical medication of claim 18, said ranitidine being present in an amount of between about 100 mg and about 150 mg.

20. A pharmaceutical medication of claim 13, said histamine H<sub>2</sub>-receptor antagonist being selected from a group consisting of famotidine and nizatidine.

21. A pharmaceutical medication of claim 13, said antacid being selected from a group consisting of aluminum hydroxide, calcium carbonate, magnesium hydroxide, sodium bicarbonate and mixtures thereof.

22. A pharmaceutical medication of claim 13, said antacid being a flavored antacid.

23. A pharmaceutical medication of claim 13, said antacid being a high potency antacid.

24. A pharmaceutical medication of claim 13, said oral medication further including an effective amount of an antifatulent.

25. A pharmaceutical medication of claim 24, said antifatulent being simethicone.

26. A pharmaceutical medication of claim 13, said antacid being aluminum hydroxide and magnesium hydroxide, and said histamine H<sub>2</sub>-receptor antagonist being cimetidine.

27. A pharmaceutical medication of claim 13, said antacid being aluminum hydroxide and magnesium hydroxide, and said histamine H<sub>2</sub>-receptor antagonist being ranitidine.

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## ORIGINAL ARTICLE

## Can famotidine and omeprazole be combined on a once-daily basis?

LARS FÄNDRIS<sup>1</sup>, HANS LÖNROTH<sup>1</sup>, ANDERS PETTERSSON<sup>2</sup> & NIMISH VAKIL<sup>3</sup><sup>1</sup>Department of Gastrosurgical Research, Sahlgrenska University Hospital, Gothenburg, Sweden, <sup>2</sup>Orexo AB, Uppsala, Sweden, and <sup>3</sup>University of Wisconsin Medical School, Madison, Wisconsin, USA

## Abstract

**Objective.** Prompt and long-standing acid control following once-daily administration of antisecretory drugs is desirable. The objective of this study was to determine whether co-administration of a well-characterized H<sub>2</sub>-receptor antagonist, famotidine, can be combined with the proton-pump inhibitor omeprazole. **Material and methods.** Intragastric 24-h pH-metry was performed in healthy, *Helicobacter pylori*-negative volunteers on day 1 and after 8 days of daily administration of 20 mg omeprazole, 10 mg famotidine, or a combination of these in a three-way crossover design. **Results.** A combination of famotidine and omeprazole raised the gastric pH level to >4 in less than 1 h. The percentage of daytime with pH >4 on day 1 was significantly higher with the combination of omeprazole and famotidine (median: 37%) than that with omeprazole alone (22%;  $p < 0.05$ ). On day 8, daytime intragastric pH >4 following treatment with omeprazole (median: 55%) or a combination of omeprazole and famotidine (61%) was superior ( $p < 0.05$ ) to that with famotidine (21%). On day 1 treatment with both famotidine and the combination (famotidine and omeprazole) showed a significantly shorter time to reach a pH of 4 (medians: 93 and 63 min, respectively) compared with treatment with omeprazole alone (173 min;  $p < 0.05$ ). **Conclusions.** Compared with treatment with omeprazole alone, on day 1 famotidine and omeprazole in combination improved the duration of and time to reach intragastric pH >4. With regard to duration with pH >4, the combination therapy was superior to famotidine alone on day 8. The rapid acid control with an H<sub>2</sub>-receptor antagonist may be combined with the long-lasting antisecretory effect of a proton-pump inhibitor.

**Key Words:** Antisecretory agents, gastric, hydrogen ions, pH, secretion, stomach

## Introduction

Histamine-2 receptor antagonists (H<sub>2</sub>-RAs) were launched during the 1970s as a development of scientific research into pharmacological extrinsic regulation of the parietal cell [1]. H<sub>2</sub>-RAs soon became clinically successful antisecretory agents but were succeeded by a new class of pharmaceuticals, the proton-pump inhibitors (PPIs) in the 1980s. These agents specifically target the membrane-bound H<sup>+</sup>/K<sup>+</sup>-ATPase within the canaliculi of the parietal cell [1–3]. One important feature of all compounds belonging to the PPI class of pharmaceuticals (as most are substituted benzimidazoles) is that they are prodrugs, and need to be protonated in order to be able to bind to and immobilize the proton pump [2,4]. The canaliculus of the gastric parietal cell is one of few compartments of the body which is acidic enough to allow such protonation and

therefore the active metabolite of the PPI is created close to its site of action. PPIs have a proven ability to offer long-term control of stomach acid and thereby cause symptom relief and healing of gastroesophageal lesions. However, owing to their mechanisms of action, the onset is relatively slow, and it usually takes several days before the maximal acid inhibitory effect is achieved [3,5]. In contrast, a single dose of an H<sub>2</sub>-RA results in significant inhibition of acid secretion within one to two hours of intake [6]. However, H<sub>2</sub>-RAs have a relatively short duration of action, and tolerance to the acid inhibitory effect gradually develops with continuous use [7]. The latter makes this class of drugs less effective for prolonged treatment. Patients with occasional symptoms of gastroesophageal reflux have been shown to have relief after intermittently administered therapy [8]. However, from the perspective

Correspondence: Lars Fändriks, Department of Gastrosurgical Research and Education, Sahlgrenska University Hospital, SE-413 45 Gothenburg, Sweden. Tel: +46 31 3424 123. E-mail: lars.fandriks@gastro.gu.se

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of rapid onset, maintained efficacy and once-daily dosage regimens, neither H<sub>2</sub>-ARs nor PPIs are optimal [2]. A tempting pharmacological approach would be to combine the rapid onset of action of a H<sub>2</sub>-RA with the more profound and long-lasting effect of a PPI. However, on theoretical grounds, it has long been suggested that concomitant treatment with an H<sub>2</sub>-RA would prevent activation of the PPI because of an increase in canalicular pH [9]. This paradigm has been challenged in intragastric pH studies that show that the bedtime addition of a H<sub>2</sub>-RA during PPI treatment decreases nocturnal reductions in pH [10]. Furthermore, in a randomized, controlled trial of H<sub>2</sub>-RAs added to PPI therapy in patients with nocturnal heartburn, a beneficial effect was shown in the first few days of treatment, consistent with an additive effect of the H<sub>2</sub>-RA [11]. In all these studies the H<sub>2</sub>-RA was administered 10–12 h after the PPI dose. Our hypothesis was that simultaneous administration of H<sub>2</sub>-RA and PPI would result in a composite effect in terms of rapid onset of acid suppression attributable to the H<sub>2</sub>-RA without loss of efficacy of the PPI. The aim of our study was to test the effect on intragastric pH of a combination therapy with a well-characterized H<sub>2</sub>-RA (famotidine) administered simultaneously with a PPI (omeprazole).

## Material and methods

### Subjects

Eight healthy, *Helicobacter pylori*-negative (as determined by [<sup>13</sup>C]-UBT (urea breath test)) [12] volunteers (mean age: 24.8 years, range 21–27 years, 2 F) were enrolled in the study. All had a normal physical examination as well as normal hematological and biochemical profiles at baseline. The subjects had no clinically significant disease, as determined by medical history. During recruitment, subjects with digestive symptoms suggestive of reflux disease or dyspepsia, and/or a previous history of gastroesophageal reflux disease (GERD) or peptic ulcers were excluded. In addition, subjects were excluded if they were hypersensitive to a PPI or H<sub>2</sub>-RA, if they were taking acid-suppressing medications or a medication likely to interact with acid secretion in the previous month, or were deemed unlikely to comply with the trial medication or investigational procedures. During the study, no concomitant therapies were allowed, with the exception of paracetamol (acetaminophen) and oral contraceptives.

### Study design

The study was designed as a single-center, open, randomized, three-period crossover trial. Each treat-

ment period was 8 days with 24-h intragastric pH-metry on day 1 and day 8. A washout period of at least 14 days was allowed between each treatment period. It follows that each subject was enrolled in the trial over approximately 12 weeks. During a treatment period, the subject ingested a 20 mg omeprazole capsule once daily, at 0900 h, (Losec; Astra-Zeneca AB, Södertälje, Sweden), or a 10 mg famotidine tablet (Pepcid; Pfizer AB, Sollentuna, Sweden), or a combination of both. Eight subjects were randomized to one of the six different treatment sequences. Six subjects completed the protocol. Smoking and alcoholic beverages were not allowed during treatment periods and food and drink intake was standardized during the 24-h pH-metry (see below).

### Treatment period procedures

The subjects arrived at the laboratory at about 0730 h having fasted overnight (i.e. no intake of food was allowed since 2400 h the previous day). A well-calibrated glass pH electrode (InMedical Gastroesophageal pH probe; Mettler-Toledo AG, Switzerland) was inserted (nasal route) into the gastric lumen and was positioned 10 cm below the esophagogastric junction. The latter was determined from the drop in pH observed during insertion, thus indicating the transition from esophagus into the gastric interior. Intraluminal pH was monitored over 24 h using a Medtronic Digitrapper pH (Medtronic A/S, Skovlunde, Denmark).

The pH-recordings started at 0830 h, with drug ingestion at 0900 h. Particular attention was paid to ensure that meals were identical in composition on each study day and ingested at fixed times. Before entering the study, each subject was allowed to choose between a limited number of dishes to be used during the subsequent study days. On each study day the individually standardized lunch (meat or fish course) was served at 1200 h. The subjects had to stay within the laboratory until and during the lunch but were then allowed to leave the hospital for home. As far as possible, the activities of daily living were similar between the study days and the subjects were asked to avoid excessive exercise. Subjects were instructed to maintain an upright position (sitting or standing) during daytime (0830 h to 2300 h).

The subjects ingested a snack (baguette) at 1600 h and had a standardized evening meal (pasta course) at 2000 h. Coffee or tea (standardized on an individual basis) was allowed along with the meals. During the 24-h pH-metry the subjects were allowed to drink standardized mineral water *ad lib* until 2400 h. The subjects returned to the laboratory at 0800 h the following morning for extubation at

0830 h, after which a second dose of the investigational compound was administered.

#### *Compliance monitoring*

After the first day, the subjects self-administered the investigational compound every morning for the next 6 days. Compliance with timing of medication ingestion was confirmed by means of camera cell-phones. Subjects sent pictures of themselves showing the investigational agent on the tongue to the investigator. The date and time were recorded by the cell-phone camera. Failure to deliver a picture before 1000 h resulted in a reminder call from the study nurse. The last dose was ingested in conjunction with a second 24-h pH recording performed on day 8 (protocol as above).

#### *Data processing and statistical analysis*

At the end of pH monitoring, the experimental data were downloaded from the digital datalogger to a personal computer in accordance with the manufacturer's instructions. The pH recordings were then analyzed using custom-made software developed at the laboratory and based on Labview (National Instruments, Austin, Tex., USA). The intragastric pH was recorded at 0.25 Hz and the median over 1 min was used in the statistical analyses. The time taken to reach an intragastric pH of  $>4$  (sustained over at least 15 min) after drug intake was analyzed. The percentage of time that the intragastric pH was above 4 was analyzed in relation to the morning period (from 0900 h to 1300 h), the daytime period (from 0900 h to 2300 h), the nocturnal period (2300 h to 06.00 h), as well as over the entire 24-h period (0830 h to 0830 h). Significant differences between groups of observations were analyzed using the Kruskal-Wallis test, and when identified, contrasted with the Mann-Whitney U-test or the Wilcoxon signed-rank test. A  $p$ -value  $\leq 0.05$  was considered significant. The statistical analyses were performed using SPSS 11 for MacOSX (SPSS Inc., Chicago, Ill, USA).

#### *Ethics*

The trials were conducted according to the principles for experimentation with human beings as defined in the Declaration of Helsinki. The study protocol was approved by the Regional Ethics Review Board in Gothenburg and all subjects were informed about the trial and signed an informed consent form.

#### **Results**

A total of 6 subjects completed the study (4 M, 2 F, mean age 24 years).

The median intragastric pH recordings over time are shown in Figure 1 along with the time of meal ingestion. The time to reach a sustained intragastric pH above 4 after ingestion of antisecretory drugs is shown in Figure 2.

On treatment day 1, both famotidine and the combination (famotidine and omeprazole) reached a pH of 4 (medians 92.5 and 62.5 min, respectively) in a significantly shorter time than treatment with omeprazole alone (172.5 min;  $p=0.041$  and  $0.002$ , respectively; Figure 2). On day 8 this difference had disappeared, as the time to reach pH  $>4$  for omeprazole alone had decreased ( $p < 0.05$ ) to a median value of 50 min, whereas the times for famotidine and the combination (famotidine and omeprazole) were not significantly different from the day 1 times (medians 82.5 and 55 min, respectively).

During the day-time period on the first treatment day, the combination treatment (omeprazole and famotidine) was associated with a significantly greater percentage of time with pH  $>4$  as compared to omeprazole alone (median values being 36.8% and 21.8%, respectively; Table I). This difference was particularly evident during the morning hours when median values were 67.1% and 27%, respectively ( $p > 0.05$ ) (Table I).

On day 8, no significant differences between treatments were observed during the morning hours (Table I), whilst daytime values for both omeprazole alone and the combination (omeprazole and famotidine) exhibited significantly longer durations of time with pH  $>4$  (median values 54.8% and 61.3%, respectively) than that with famotidine alone (median value 21.4%).

Viewed over 24 h, no differences were found between treatments on day 1, whereas the percentages of time with pH  $>4$  were significantly greater after treatment with either omeprazole or the combination of omeprazole and famotidine (medians 43.6 and 46.7, respectively) than the percentage of time after treatment with famotidine (median value 16.9%).

As expected from the moderate doses of each drug given, the percentage time spent above pH 4 during the night was low on day 1, irrespective of treatment (group medians ranging between 1.7 and 3.7) (Table I). On day 8 the nocturnal values were higher after treatment with omeprazole as well as after the combination of omeprazole and famotidine (medians 13.5 and 17.1%, respectively), but in relation to day 1, these differences did not attain statistical significance.



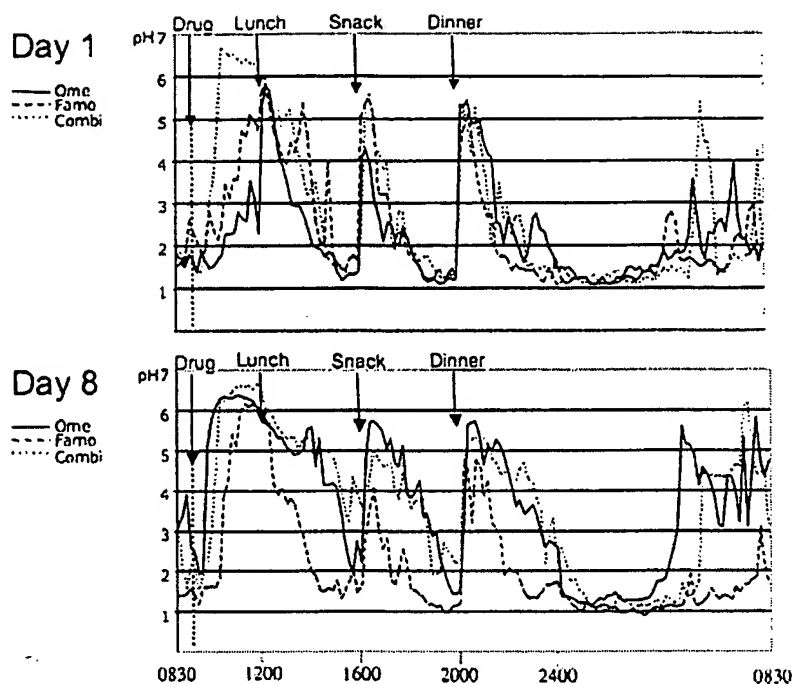


Figure 1. Intra-gastric 24-h pH-metry on day 1 (upper panel) and day 8 (lower panel) of treatment periods with omeprazole 20 mg (Ome), or famotidine 10 mg (Famo), or a combination of both (Combi). Values are plotted as the median pH of all values obtained at that time-point ( $n = 6$ ).

## Discussion

The ideal pharmacological agent for on-demand treatment of acid-related symptoms should combine a rapid onset of acid inhibition with a sustained effect on acid secretion. The need for rapid relief of symptoms is obvious but patients with intermittent symptoms tend to take medications for several days, suggesting that continued acid inhibition is important for symptom control [13]. Combining  $H_2$ -RAs with PPIs is controversial on theoretical grounds but there is a paucity of published information demonstrating the effect of the combination on intra-gastric pH. It has been suggested that the efficacy of a PPI may be adversely affected by simultaneous and rapid inhibition of the acid-producing machinery with another agent. PPIs are weak bases and accumulate in the acidic compartments of the parietal cell where they are protonated to a sulfenamide form, which, in turn, reacts covalently with cysteine moieties of the proton pump [2,4]. This reaction has recently been shown to involve protonation in two steps, with one  $pK_a$  around 4 and a second  $pK_a$  estimated to be between 0.6 and 0.8 [4]. On theoretical grounds, an acid inhibitor, if its effects were profound enough, could alter the pH in the acid space, decreasing protonation of the PPI and reducing its efficacy [8].

The results of this study are novel because they indicate that acid inhibition with an  $H_2$ -RA does not affect the antisecretory activity of omeprazole. This

is probably because the effect of currently available drugs on canalicular pH is smaller than the effect on intra-gastric pH. This is why, when administered for long periods of time, potent PPIs retain their efficacy, because protonation in the canalicular space continues despite a reduction in the volume of gastric secretion and an increase in intra-gastric pH [2]. Consequently, clinically used doses of  $H_2$ -RAs are also unlikely to affect canalicular pH because they are less potent inhibitors of acid secretion. This is supported by the present study, which did not detect any significant difference between the antisecretory effect after 8 days of treatment with omeprazole alone or in combination with famotidine. However, the absence of any difference should not be interpreted to mean that the two treatment regimens are of equal efficacy. Demonstration of therapeutic equivalence demands another study design and a larger study population; an investigation of this kind has yet to be undertaken.

Tolerance to  $H_2$ -RAs following continued administration is a well-known phenomenon [7]. Tolerance to famotidine is reported to occur after 14 days of continuous administration and probably develops during the second week of administration [14]. This is supported by Furuta et al. who reported no tolerance during a 7-day treatment period using 20 mg famotidine twice daily [15]. In the present

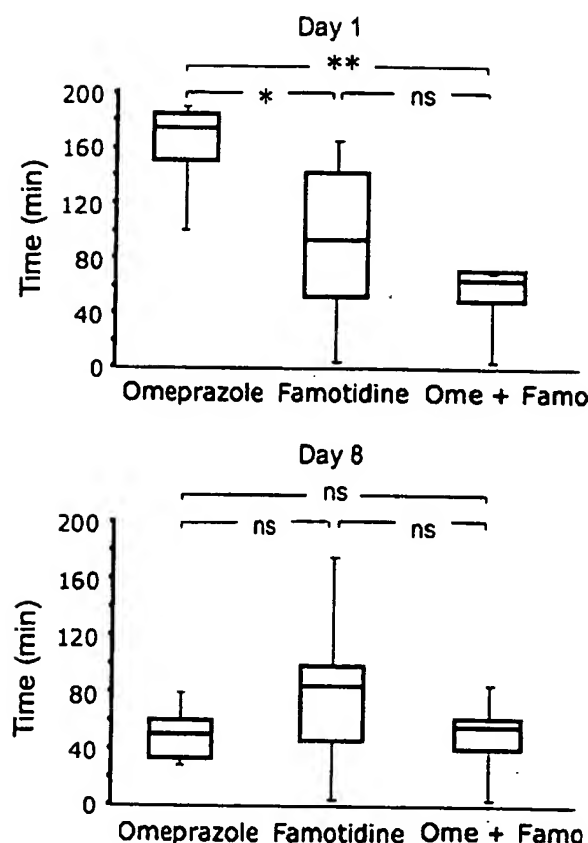


Figure 2. Box-and-whiskers plot showing the time to reach a sustained (at least 15 min) pH above 4 following oral intake of omeprazole 20 mg, or famotidine 10 mg, or a combination of both (Ome+Famo). Median values are indicated as a transverse line within the box, the interquartile range as the vertical extent of the box and the total range as the whiskers ( $n=6$ ). Significant differences are indicated by asterisks (\* $p < 0.05$ ; \*\* $p < 0.01$ ).

study we also did not find any significant loss of efficacy with famotidine after a week of administration. However, it should be remembered that, compared with famotidine alone, the combination with omeprazole was superior with regard to daytime and 24-h duration of intragastric pH  $> 4$ .

Improving the speed of onset of currently available PPIs is an important target of new drug development, and a newly described class of acid inhibitors (potassium-competitive acid blockers) offer significant advantages with speed of acid inhibition [16–18]. Clinical trials on these agents have, however, not shown clinical superiority, and hepatotoxicity has been a problem with at least one agent [19]. The clinical implications of a drug combination that combines the speed of an  $H_2$ -RA and the sustained effect of a PPI are intuitive. Rapid relief of meal-induced heartburn would occur with the  $H_2$ -receptor component and a more sustained effect on acid inhibition would occur from the PPI [20]. Such an agent could be useful with on-demand therapy. Another potential application is in individuals who have breakthrough symptoms on receiving PPI therapy. Rapid control of pH is also potentially useful in *H. pylori* treatment regimens. If the pH is raised early in combination treatment regimens, such as PPI triple therapy, the bioavailability of antibiotics may be increased by decreasing gastric volume and viscosity and other effects which could enhance eradication of *H. pylori* infection [21]. Further clinical trials are necessary to determine the effects of combination therapy on symptoms and on the speed of symptom response.

In summary, the present investigation shows that a once-daily administration of the  $H_2$ -RA famotidine combined with the PPI omeprazole results in a

Table 1. Percentage of time with gastric pH above 4 on days 1 and 8 of treatment with omeprazole 20 mg (ome), or famotidine 10 mg (famo), or a combination of both treatments (combi) o.d.

|           | % Time with pH $> 4$          |                  |                               |
|-----------|-------------------------------|------------------|-------------------------------|
|           | Ome                           | Famo             | Combi                         |
| Day 1     |                               |                  |                               |
| Morning   | 27 (24.8–31.6)                | 54 (36.9–69.5)   | 67.1 (63.4–77)*               |
| Daytime   | 21.8 (19.8–24.4)              | 34.4 (22.7–50.9) | 36.8 (30.9–46.5)              |
| Nocturnal | 3.7 (2.4–10.4)                | 2.9 (0.5–8.0)    | 1.7 (0.1–8.0)                 |
| 24-h      | 17.0 (15.5–23.7)              | 28.0 (19.2–33.6) | 27.6 (22.3–31.0)              |
| Day 8     |                               |                  |                               |
| Morning   | 77.7 (58.3–83.3)              | 48.3 (38.5–71.9) | 78.1 (74.9–79.8)              |
| Daytime   | 54.8 (53.9–58.5) <sup>#</sup> | 21.4 (18.7–28.5) | 61.3 (60.9–62.1) <sup>@</sup> |
| Nocturnal | 13.5 (7.7–20.1)               | 2.4 (0.5–12.6)   | 17.1 (12.3–22.2)              |
| 24-h      | 43.6 (39.5–50.3) <sup>#</sup> | 16.9 (14.2–27.9) | 46.7 (43.4–50.2) <sup>@</sup> |

Values are given as medians (interquartiles). Morning: 0900 h to 1300 h; daytime: 0900 h to 2300 h; nocturnal: 2300 h to 0600 h; 24-h: 0830 h to 0830 h.

\* $p = 0.002$  versus omeprazole alone; <sup>#</sup> $p < 0.05$  versus omeprazole alone; <sup>@</sup> $p < 0.05$  versus famotidine; <sup>@</sup> $p < 0.05$  versus famotidine. All other comparisons – not significant.

prompt improvement of acid control in onset and efficacy as compared with either drug given alone. Further studies are needed to determine whether combination therapy offers advantages in the clinical setting.

### Acknowledgements

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# The effect of over-the-counter ranitidine 75 mg on night-time heartburn in patients with erosive oesophagitis on daily proton pump inhibitor maintenance therapy

N. VAKIL\*, N. GUDA\* & S. PARTINGTON\*†

\*University of Wisconsin Medical School, Milwaukee, WI; †Center for Urban Population Health, Milwaukee, WI, USA

Correspondence to:

Dr N. Vakil, Aurora Sinai Medical Center, 945 North 12th Street, Room 4040, Milwaukee, WI 53233, USA.  
E-mail: nvakil@wisc.edu

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## SUMMARY

### Background

H<sub>2</sub>-receptor antagonists are widely used with proton pump inhibitors.

### Aim

To determine if H<sub>2</sub>-receptor antagonists used in conjunction with proton pump inhibitors were effective for nocturnal heartburn in patients taking proton pump inhibitors.

### Methods

We evaluated 386 patients with erosive oesophagitis documented at endoscopy who were receiving single daily maintenance proton pump inhibitor therapy to determine if they had symptoms of nocturnal heartburn. Patients with two or more episodes of night-time a week were invited to participate in the study. Patients were randomly assigned to a single dose of an over-the-counter preparation of ranitidine 75 mg at bedtime or matching placebo for 14 days.

### Results

The prevalence of nocturnal symptoms was 10.6%. Mean symptom scores on the first day of the trial (baseline) were similar between the treatment group ( $1.1 \pm 0.9$ ) and the placebo group ( $1.1 \pm 1.1$ ). On day 3, symptom scores were significantly lower in the ranitidine group ( $0.71 \pm 0.69$ ) compared with the control group ( $1.4 \pm 1.2$ ;  $P = 0.045$ ). On day 14, mean symptom scores were similar in the ranitidine group ( $0.82 \pm 0.95$ ) and the control group ( $1 \pm 0.84$ ).

### Conclusions

Nocturnal heartburn is uncommon on proton pump inhibitor therapy; the addition of ranitidine at bedtime resulted in a decrease in symptom scores on day 3 but there were no differences on day 14.

*Aliment Pharmacol Ther* 23, 649–653

## INTRODUCTION

Night-time heartburn is a common symptom in untreated patients with reflux disease and has a significant impact on quality of life. Reflux during the nocturnal period may also have significant consequences as protective mechanisms such as peristalsis are inhibited during sleep. Acid contact time may therefore be higher at night and the adverse consequences of nocturnal reflux may be potentially greater. Recent studies that measure intragastric pH in individuals on once daily or twice daily therapy with proton pump inhibitors (PPI) have shown that there is a significant drop in intragastric pH at night in some subjects, despite PPI therapy. Intragastric pH studies have also demonstrated that the addition of a small dose of a histamine-2 ( $H_2$ )-receptor antagonist at bedtime can decrease or abolish the nocturnal drop in intragastric pH. There is little information, however, on the prevalence of nocturnal heartburn in patients taking regular PPI therapy for gastro-oesophageal reflux disease (GERD) and no data on the effectiveness of  $H_2$ -receptor antagonists in controlling nocturnal symptoms in this group of patients. We therefore performed a randomized placebo-controlled trial that evaluated the efficacy of bedtime  $H_2$ -receptor antagonist therapy in the treatment of nocturnal heartburn in patients taking daily PPI therapy.

## METHODS

We evaluated 386 patients with erosive oesophagitis documented at endoscopy who were receiving daily maintenance PPI therapy to determine if they had symptoms of nocturnal heartburn. Patients were identified from a database and contacted to determine if they had nocturnal heartburn. Patients presenting for annual follow-up visits on maintenance therapy with PPIs were also interviewed and offered entry if eligible. All patients had received at least 8 weeks of the same dose of the PPI. All patients were taking a single daily dose of the PPI half an hour before breakfast daily. Patients with two or more episodes of night-time a week were invited to participate in the study.

After written informed consent was obtained, the patients were randomly assigned to a single dose of an over-the-counter preparation of ranitidine tablets 75 mg (Pfizer Consumer Healthcare, Morris Plains, NJ, USA) at bedtime or matching placebo for 14 days. Randomization was performed using a random number

chart with concealed allocation using opaque envelopes so that neither the investigator nor the patient was aware of the medication they were receiving. Proton pump inhibitor therapy remained unchanged in timing and dose. Daytime heartburn was evaluated using a validated 4-point Likert scale (none, mild, moderate, severe) for heartburn severity at baseline and every morning at the approximately the same time for the 14 days of the trial. Nocturnal heartburn was measured daily as a dichotomous response (yes/no) because severity measures are of limited utility in the nocturnal period because of recall bias.

## Statistics

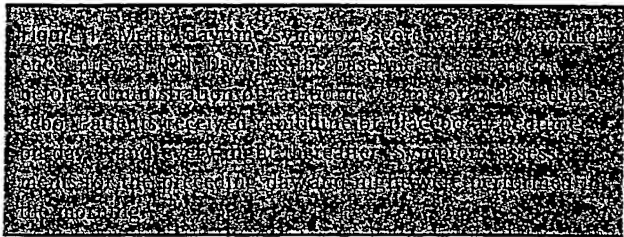
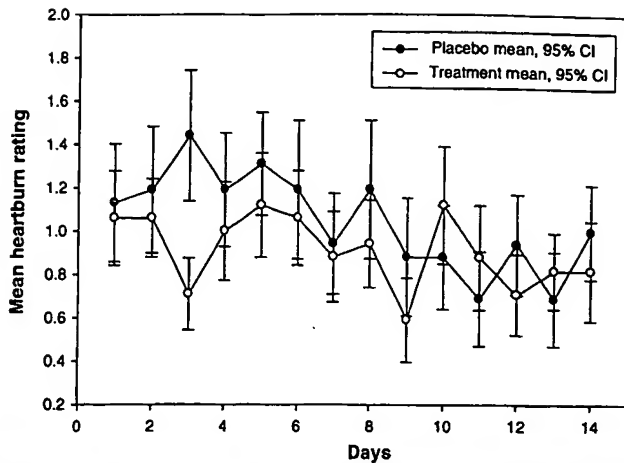
Results are presented as mean values of the 4-point scale for daytime heartburn and proportion responding yes for nocturnal heartburn with 95% confidence intervals. Planned comparisons were made between the groups at baseline (day 1) on day 3 and day 14. These time points were chosen because intragastric pH data suggest that the effect of adding  $H_2$ -receptor antagonists is pronounced in first week of therapy but the effect disappeared after more prolonged use.

## Human subjects

The human subjects review board at Aurora Sinai Medical Center, approved the protocol and all participating patients gave written informed consent (the study was sponsored by Pfizer Inc.).

## RESULTS

Forty-one of the 386 patients (10.6%) surveyed had nocturnal symptoms of heartburn at least twice a week. By self-report, all patients were taking their PPIs daily half an hour before breakfast. All 41 had erosive oesophagitis demonstrated at endoscopy prior to the initiation of PPI therapy (Los Angeles A or B in 40 patients and Los Angeles grade C in one patient). The prevalence of nocturnal symptoms in this population was 10.6%. Thirty-three of the 41 patients agreed to participate in the study. The remaining eight patients wished to have additional therapy without the possibility of receiving a placebo and refused to participate. Sixteen patients were randomized to placebo and 17 patients were randomized to ranitidine 75 mg at bedtime. At baseline, seven of 16 patients in the placebo



group and eight of 17 in the ranitidine group reported symptoms of nocturnal heartburn. Mean symptom scores did not change significantly over time and there were no significant differences between the groups. Mean daytime symptom scores on the first day of the trial (baseline) were similar between the treatment

group ( $1.1 \pm 0.9$ ) and the placebo group ( $1.1 \pm 1.1$ ). On day 3, symptom scores were significantly lower in the ranitidine group ( $0.71 \pm 0.69$ ) compared with the control group ( $1.4 \pm 1.2$ ;  $P = 0.045$ ; Fig. 1). On day 14, mean symptom scores were similar in the ranitidine group ( $0.82 \pm 0.95$ ) and the control group ( $1 \pm 0.84$ ; Fig. 1). There were no significant differences in proportion of subjects reporting nocturnal heartburn between the two groups (Fig. 2).

## DISCUSSION

Nocturnal symptoms of heartburn are common in the general population and have been shown to be associated with a significant decrease in the quality of life. There is little information on the prevalence of nocturnal heartburn in patients with erosive oesophagitis who are receiving PPI therapy. The results of this study show that nocturnal heartburn is reported by approximately 10% of patients with erosive oesophagitis on PPI therapy. This is probably an underestimate of the number of patients who actually have nocturnal reflux because many reflux episodes are not recognized or reported by the patient.<sup>1</sup> Our study population was chosen to be well-characterized and therefore only patients with previously documented erosive oesophagitis were studied. The prevalence of nocturnal symptoms may be different in other populations of patients with reflux symptoms, e.g. non-erosive reflux disease.

We studied Zantac 75 tablets as this preparation is widely available over-the-counter throughout the world (the USA, Canada, Australia, New Zealand, Denmark, the UK) and is frequently used by patients for control of heartburn. In a recent report on the over-the-counter acid-blocker drugs, ranitidine 75 was one of the top three (along with famotidine and omeprazole) over-the-counter acid inhibitors purchased in the United States.<sup>2</sup> We also chose low-dose ranitidine because it has been shown to be effective in increasing nocturnal intragastric pH and because it can have an effect that can be detected up to 15 h after a single dose in gastric pH studies.<sup>3</sup> In some studies ranitidine 75 mg has been more effective than famotidine 10 mg and its effects on pH were more pronounced in the first 2.5 h after dosing.<sup>4</sup> Robinson *et al.* studied a group of patients with heartburn who were given a single daily dose of omeprazole and demonstrated that addition of bedtime ranitidine in a dose of 75 mg eliminated night-time gastric acidity but oesophageal

acid exposure was not significantly changed because the patients no longer had nocturnal acid exposure in the oesophagus after receiving omeprazole.<sup>5</sup> In another intragastric pH study, bedtime ranitidine (150 mg) was more effective than bedtime omeprazole in controlling night-time acid in normal subjects.<sup>6</sup> In GERD patients, addition of an H<sub>2</sub>-receptor antagonist to a regimen of twice a day omeprazole therapy improved intragastric pH values.<sup>7</sup> None of these studies, however, established a clear link between changes in intragastric pH and intraoesophageal pH or symptoms. Ours *et al.* studied GERD patients randomized to four treatments: (i) omeprazole 20 mg twice daily for 2 weeks; (ii) omeprazole 20 mg twice daily for 2 weeks with ranitidine 300 mg at bedtime for 4 weeks; (iii) omeprazole 20 mg before breakfast and before dinner for 2 weeks and (iv) omeprazole 20 mg every 8 h for 2 weeks. Although all the regimens improved intragastric pH parameters compared with baseline, no single treatment regimen resulted in more significant suppression of nocturnal acid than the others. Oesophageal acid reflux and patient symptoms were well controlled despite acid being present in the stomach.<sup>8</sup> In another pH study, addition of ranitidine 150 mg at bedtime did not alter oesophageal acid exposure during sleep in patients taking omeprazole 20 mg twice daily.<sup>9</sup> In a long-term study of the effects of adding H<sub>2</sub>-receptor antagonists to a regimen of PPIs, Fackler *et al.* showed that intragastric pH values improved in patients receiving H<sub>2</sub>-receptor antagonists but that these effects were short-lived and were no longer apparent at 1 week presumably because of the development of tachyphylaxis.<sup>10</sup>

Drug tolerance is said to have occurred when, after prior exposure to a drug, an individual requires an unusually large dose of that drug to achieve the usual effect.<sup>11</sup> Tolerance to H<sub>2</sub>-receptor antagonists has been studied in healthy volunteers and in patients with duodenal ulcer. In volunteers, the reduction in acid inhibition is related to the dose of the H<sub>2</sub>-receptor antagonist administered.<sup>12</sup> Despite the absence of clinical data on symptoms in patients with GERD, the concept of adding H<sub>2</sub>-receptor antagonists to PPI therapy has gained wide attention and these combinations of therapy are frequently prescribed by primary care doctors.<sup>13</sup> Our study demonstrates that symptom scores improve at day 3 but the effect is short-lived and is not seen on day 14. The greatest loss of efficacy in acid inhibition in intragastric pH studies in volunteers is in the first

few days after initiation of therapy and is well-established by 1 week.<sup>11</sup> Our results are therefore in keeping with pH studies. From a clinical standpoint, one may interpret our data and the available intragastric pH data to suggest that there is short-term efficacy in nocturnal heartburn relief with over-the-counter doses of H<sub>2</sub>-receptor antagonists. Given the clinical profile of these agents the optimal use of an H<sub>2</sub>-receptor antagonist in a patient taking a PPI would be in intermittent courses that are <1 week in duration. Continuous use is probably associated with the development of tolerance and a disappearance of the clinical effect. Because of the rapidity with which the H<sub>2</sub>-receptor antagonists act, they seem well suited for patients who are generally well maintained on PPI therapy but develop nocturnal heartburn under special circumstances, e.g. a late evening meal or the ingestion of alcohol with the meal. In these instances, tolerance would not play a role as the H<sub>2</sub>-receptor antagonist would be taken infrequently when these specific circumstances arose. In this context, H<sub>2</sub>-receptor antagonists have another advantage in that they are rapidly effective even when taken after a meal.<sup>14</sup> Finally, theoretical concerns that the H<sub>2</sub>-receptor antagonist might affect next day activity of PPIs have been allayed by pH studies which have shown no effect on next day acid control with the PPI.<sup>15</sup> Other preparations of over-the-counter medications are also available such as the effervescent formulation of ranitidine 75. These compounds have a more rapid onset of effect and may offer further advantages in symptom relief but were not evaluated in this study.<sup>16</sup>

Our study has some limitations. The numbers of patients randomized are small and this was due to the paucity of patients reporting nocturnal heartburn on single daily doses of PPIs. The possibility of a type 1 error exists but a small effect on symptoms is probably of little clinical significance. Our study is, however, the only randomized-controlled trial addressing symptoms with this combination of drugs. We believe that a more thorough appraisal of combination therapy is necessary before it becomes widely used in clinical practice. Such studies would have to consider a higher dose of an H<sub>2</sub>-receptor antagonist but the development of tolerance is still a problem with these agents.<sup>17</sup> Our study also points out the limitations of intragastric pH studies when they are extrapolated to clinical conditions. These studies are performed with an intragastric pH



electrode that measures pH but does not measure gastric volume. Therefore, these studies do not necessarily predict intraoesophageal pH changes or the development of symptoms.

## ACKNOWLEDGEMENT

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# Symptom evaluation in reflux disease: workshop background, processes, terminology, recommendations, and discussion outputs

J Dent, D Armstrong, B Delaney, P Moayyedi, N J Talley, N Vakil

*Gut* 2004;53(Suppl IV):iv1-iv24. doi: 10.1136/gut.2003.034272

There has been no published indepth systematic evaluation of the best approaches to symptom evaluation in gastro-oesophageal reflux disease (GORD). A two day international multidisciplinary workshop was therefore held in Marrakech, Morocco, in September 2002 to address these issues. The aim of the workshop was to critically review the data regarding the reliability, processes, and priorities for symptom evaluation in GORD patients. The workshop was designed to give outputs that could be readily reported and to arrive at specific recommendations on best practice in symptom evaluation in reflux disease.

of symptoms is predictive of healed oesophagitis during short and long term therapy but there are few data on predictors of a symptomatic response to therapy.

Disease specific measures of quality of life, such as the quality of life in reflux and dyspepsia (QOLRAD) scale, are more responsive to change than generic measures such as SF-36 and EuroQol. However, generic measures do allow comparison with other diseases. Quality of life should at least be measured at the beginning and end of a trial, with at least annual measurement in long term trials.

Patient satisfaction depends on several factors, including the outcome of treatment, process of care, and the patient-doctor relationship. There are no validated instruments to measure patient satisfaction in this disease, and there is little information on patient expectations.

## SUMMARY

To date, there has been no published indepth systematic evaluation of the best approaches to symptom evaluation in gastro-oesophageal reflux disease (GORD). A two day international multidisciplinary workshop was therefore held in Marrakech, Morocco, in September 2002, to address this. The workshop focused on four key topics and the outcomes are reported here.

- (1) Diagnostic use of symptoms.
- (2) Assessment of reflux symptom severity.
- (3) Quality of life.
- (4) Patient expectations and satisfaction.

In addition, recommendations were made on the terminology to be used in this area.

GORD should be defined by the presence of reflux oesophagitis (Los Angeles grades A-D) and/or when it causes reflux symptoms that are sufficient to impair quality of life and/or when it is associated with a risk of long term complications. Moderate symptoms that occur more than once per week impair quality of life and can therefore be considered as GORD. The best method of eliciting the predominant symptom is with a technically adequate clinical interview. Consensus was reached that dysphagia should be investigated if the pattern and duration were appropriately characterised.

For short term therapy, absence of heartburn, self-assessed by the patient using a seven point modified Likert scale over a one week period, is considered to be an optimal objective end point. Regurgitation should also be monitored. Absence

## BACKGROUND TO THE WORKSHOP

The last 15–20 years have seen major advances in the understanding of GORD and major development of pharmacological, surgical, and luminally delivered physical therapies. There has been a commensurate burgeoning of clinical trials into reflux disease therapies, driven mainly by the very high prevalence of this problem in developed countries, and the rapid evolution of therapeutic options.

The overall quality of clinical trials into reflux disease has improved greatly in the last 15–20 years but there is still considerable potential for making such trials more authoritative and comparable. This potential now resides predominantly in approaches to symptom evaluation.

Symptom evaluation is a crucial aspect of both the routine clinical management and the clinical trialling of reflux disease. Diagnosis and pre-treatment severity assessment rest heavily on symptom evaluation, as does assessment of the outcomes of therapy. With some therapies, effective screening for side effect symptoms is an important part of the measurement of therapeutic outcomes.

Despite the importance of symptom evaluation in reflux disease, there has been no published indepth systematic evaluation of the best

**Abbreviations:** GORD, gastro-oesophageal reflux disease; QOLRAD, quality of life in reflux and dyspepsia; PPI, proton pump inhibitor; VAS, visual analogue scales; GSRS, gastrointestinal symptoms rating scale; PGWBI, psychological general well being index; ENT, ear, nose, and throat; RSI, reflux symptom index; RFS, reflux finding score; QALYs, quality adjusted life years

See end of article for authors' affiliations

Correspondence to: Professor J Dent, Department of Gastroenterology, Hepatology, and General Medicine, Royal Adelaide Hospital, Adelaide, Australia; jdent@mail.ra.h.sa.gov.au

**Table 1** Grading of the nature of the evidence for each workshop proposition

| Nature of evidence | Study design   | Study execution                                 | Consistency | Directness of evidence    |
|--------------------|--|---|-------------|---------------------------|
| A                  | Meta-analysis of RCTs* (for interventions)<br>RCTs (for interventions)   | No important flaws                              | Consistent  | Direct or strong indirect |
| B                  | Non-randomised studies (for diagnosis and prognosis)<br>Meta-analysis of RCTs or RCTs (for interventions)      | Important flaw or inconsistent or weak indirect |             |                           |
| C                  | Non-randomised controlled studies (for interventions)<br>Non-randomised controlled studies (for interventions) | Important flaw or inconsistent or weak indirect | Consistent  | Direct or strong indirect |
| D                  | Meta-analyses or RCTs with a combination of important flaws and inconsistency and/or indirect evidence         | No important flaws                              |             |                           |
| E                  | Other evidence (not expert opinion)<br>Expert opinion  | Important flaw or inconsistent or weak indirect |             |                           |

\*RCTs, randomised controlled trials.

Adapted from: Mason J, Eccles M. *Guideline Recommendation and Evidence Grading (GREG): a new grading method for Clinical Guideline Development Groups*. University of Newcastle upon Tyne: Centre for Health Services Research, 2003; report 109.

Exceptions that can alter the quality of grading: sparse data (few events); use of data not in its initial randomisation, or apparent publication bias, can lower the quality; a very strong association can raise the quality.

Coding notes: important flaws occur when the highest standards of research that could be achieved by a study are not applied; consistency occurs at two levels—design (consistent methods, patients, outcomes) and statistical (a test of homogeneity of a summary estimate when the level of design consistency is acceptable and meta-analysis appropriate); directness: "direct evidence": relevant patient benefits and harms are measured in studies; "strong indirect": the surrogate end point is strongly related to desirable and points, or that direct evidence is available for a sufficiently related patient group; "weak indirect": the relationship between the study outcomes and patient benefits or harms is insufficient.

approaches to this for routine practice and clinical trials. This lack of considered guidance is evident in the design of published clinical trials that use a wide range of terminologies and approaches to symptom evaluation. Not all of the methods used can be optimal for identification of suitable patients for enrolment in clinical studies and for assessment of therapeutic outcomes. The diversity of approaches used also makes it difficult or impossible to make detailed comparisons among trials, or to safely pool symptom data from different clinical trials.

The potential for further enhancement of the quality of clinical trials in reflux disease led to the holding of a two day international multidisciplinary workshop in Marrakech, Morocco, in September 2002, that is the subject of this report. This evaluated both the general principles and the particulars of symptom evaluation in reflux disease for routine clinical care and clinical trials. The aim of the workshop was to critically review the data regarding the reliability, processes, and priorities for symptom evaluation in GORD patients. The workshop was designed to give outputs that could be readily reported and to arrive at specific recommendations on best practice in symptom evaluation in reflux disease.

## Workshop processes

### Structure of the workshop

The workshop involved 28 participants from 10 countries, who were specialist gastroenterologists, primary care physicians, surgeons, and researchers who have a major involvement in managing and/or researching reflux disease, and/or researching more general fields of methodology relevant to the topic.

Following reviews of generic methodological issues, the workshop was divided into four sequential sessions, focusing on the following topics:

- (1) diagnostic use of symptoms;
- (2) assessment of reflux symptom severity;
- (3) quality of life;
- (4) patient expectations and satisfaction.

Each session opened with an overview of the clinical practicalities and a methodological review relevant to the session, followed by division of the participants into four concurrent discussion subgroups, and then a plenary discussion and voting session.

Propositions were prepared focusing on specific issues, and were assigned to individual participants to research in advance of the workshop. Participants presented a review of the data relevant to their assigned proposition in a discussion subgroup where the proposition was then discussed and voted on (see below). The conclusions of the subgroup on each of their assigned propositions were presented to the full workshop in the plenary session, further discussion occurred as necessary, and all participants then voted anonymously on the proposition, this time electronically (see below).

After these four main workshop sessions, a final session was devoted to discussion of the major workshop conclusions and outcomes, with voting on further propositions as necessary to clarify outstanding questions and issues.

### Process, format, and reporting of voting

For each proposition, participants in the discussion subgroup agreed on the nature of evidence for the proposition, after discussion of the study design and execution, consistency of the findings, and directness of the evidence (table 1). They then voted on the strength of their recommendation of the proposition (table 2). Both the nature of evidence that had been agreed and the strength of the recommendation from the discussion subgroup were presented to the full workshop in the plenary session. After discussion in the plenary session, all participants voted on the strength of the recommendation (table 2).

The outcome of voting from the plenary session is provided in this manuscript for each proposition in each of the four different topic sessions. The proposition is given in bold italics, followed by the nature of evidence agreed by the subgroup, which is given in italics. The strength of recommendation is then given, expressed as the percentage of participants voting at each level. The level of recommendation receiving the largest vote is highlighted in bold.

**Table 2** Levels of strength of recommendation used in voting on the workshop propositions

| Strength of recommendation |
|----------------------------|
| Agree strongly             |
| Agree with reservation     |
| Disagree with reservation  |
| Disagree strongly          |

Each proposition is followed by a discussion of the major points raised in both the subgroups and the plenary session, together with the relevant references. Additionally, editorial commentary and opinion is given from the editors of this report who were also the Core Group responsible for the planning of the workshop, including preparation of the propositions. In addition to the reporting of the voting, discussion, and editorial comment on the workshop propositions given in this manuscript, individual manuscripts authored by the presenters of methodological reviews within the workshop are given in the rest of the workshop report.

### Considerations involved in judging the nature of evidence and strength of recommendation

In any evidence based guideline, there needs to be an objective and transparent process by which the strength of evidence and the strength of a recommendation are graded. The two are not directly linked, as there may be other powerful factors, such as affordability, lack of evidence of long term efficacy, or lack of international generalisability that may influence the interpretation of evidence. Workshop participants were reminded that, in general, the more explicit and detailed the questions asked about the validity of the evidence presented, the more that evidence should weigh in the decision. The evidence grading used in the workshop is an example of this more explicit testing, incorporating domains for design and execution of the study, the consistency of the effect, and allowing for non-randomised designs where these are the appropriate method.

A properly conducted randomised controlled trial is the best method of avoiding bias when comparing two interventions, but where prognosis or diagnosis is concerned, a well designed cohort study is the choice. Furthermore, where good evidence of an indirect nature (for example, for a proxy outcome and mortality) can be linked, grade A was also given (table 1). Flaws, lack of consistency, inappropriate outcome measures or settings, and lack of direct linkage drop the level of evidence. In general, sample size was explored using confidence intervals as a measure of precision but large numbers of small studies are more prone to publication bias and bias due to poor design; participants were cautioned against this.

### Additional data analyses for the workshop

As part of their preparation for the workshop, participants were given access to the AstraZeneca reflux disease clinical trial database. Further exploratory analyses were made on this large database where relevant. Where the results of such analyses have been used as evidence, this is noted in the report. The findings of such secondary analyses are identified and referenced to the original study publication.

### TERMINOLOGY ISSUES AND RECOMMENDATIONS

One output of the workshop was a recommendation for consistent use of simplified terminology for symptom evaluation in GORD. The terminology used in the area of symptom evaluation in reflux disease is highly varied, and in many cases is vague. A systematic review has been conducted

of randomised clinical trials of medical therapies in reflux disease, which includes over 200 publications (see Sharma and colleagues<sup>1</sup> in this supplement (*page iv58-iv65*)). Analysis of these trials highlights some 20 different terms used to describe the absence of GORD symptoms, and several terms to describe a reduction in symptoms (table 3). Moreover, there is significant overlap in what these terms are considered to mean, "symptom relief", for example, being used variously to describe absence of symptoms as well as reduction in symptoms. There is also considerable heterogeneity in how terms are defined. Some of the terminology used involves poor use of the English language. For instance, some terms are used that are internally contradictory when their pure meanings are considered (for example, "complete relief"). This is often because qualifiers are attached to words that are intended to convey absolute measures. Similarly, there is also variation in the terminology used to describe regurgitation (table 4).

The survey of the use of terminology highlights the need for consistent use of unambiguous terms that describe symptom status in reflux disease. There is a clear need for greater consistency and definition of terms, not least to facilitate comparisons among different studies. Use of the same terms, with the same meanings, would be a significant step forward. The time available for the workshop did not allow detailed consideration of these issues of terminology. The authors of this section of the report, who were also the Core Group responsible for its planning, therefore met after the workshop to consider issues of terminology and make recommendations that simplify, and define, the terminology to be used. These recommendations have been applied throughout this workshop report.

### Recommendations for improved terminology

#### When a symptom is not present

"Absence" is the recommended term to state that a symptom is not present. It is interchangeable with "symptom free/free of symptoms". These terms were selected on the basis of simplicity, minimal ambiguity, and being most readily understood in other languages. This terminology needs to be used in conjunction with specification of the symptom in question (for example, heartburn) and a qualifier of the timescale or duration (for example, "absence of heartburn for

**Table 3** Terms used to describe the absence or reduction of gastro-oesophageal reflux disease symptoms in studies assessed for the systematic review by Sharma and colleagues<sup>1</sup> in this supplement (*see page iv58-iv65*)

| Absence of symptoms                | Reduction of symptoms |
|------------------------------------|-----------------------|
| Symptom free                       | Symptoms improved     |
| Completely symptom free            | Symptom relief        |
| Persistently symptom free          | Clinical improvement  |
| Totally symptom free               |                       |
| Symptom relief                     |                       |
| Profound symptom relief            |                       |
| Complete symptom relief            |                       |
| Symptom resolution                 |                       |
| Complete symptom resolution        |                       |
| Sustained symptom resolution       |                       |
| Symptom remission                  |                       |
| Symptoms ceased                    |                       |
| Symptoms absent                    |                       |
| Symptoms eliminated                |                       |
| Persistent absence of symptoms     |                       |
| Disappearance of symptoms          |                       |
| Asymptomatic                       |                       |
| Complete disappearance of symptoms |                       |
| No symptoms                        |                       |
| Completely gone                    |                       |

**Table 4** Terms used to describe the symptom of regurgitation in studies assessed for the systematic review by Sharma and colleagues<sup>1</sup> in this supplement (see page iv58–iv65)

|                                  |
|----------------------------------|
| Regurgitation                    |
| Acid regurgitation               |
| Gastro-oesophageal regurgitation |
| Acid eructation                  |

the last seven days", or "heartburn free for the last seven days", or "free of heartburn for the last seven days".

**When a symptom persists to some degree**

"Reduction/reduced" is recommended to describe when a symptom has decreased but is still present to some extent. A baseline comparator is implicit in this. The term "relief" was rejected as it was seen to be too open to interpretation (see above). When "relief" is used to describe a reduction of a symptom, it is a term that implies a judgement by the patient as to whether the reduction reaches a threshold. This could vary among patients according to the patient's expectations and level of satisfaction with therapy, potentially suggesting that a patient is satisfied with their symptom status when, in fact, they are still suffering significant residual symptoms.

**When a symptom worsens**

"Increase" is the recommended term to describe worsening of a symptom. This may occur, for example, when there is an increase in a specific symptom or symptoms as a side effect of therapy.

**Specification of the symptom(s)**

The symptom(s) in question should always be specified, with the four main symptoms being "heartburn", "regurgitation", "epigastric pain", and "dysphagia", along with the descriptors that describe presence/absence and intensity. Terms to describe regurgitation were considered, as there is some heterogeneity in this. "Acid regurgitation", "gastro-oesophageal regurgitation", and "acid eructation" were all rejected, not least because the content of what is regurgitated cannot be defined based on symptoms. The recommended term is thus "regurgitation". This needs to be clearly distinguished from "water brash".

The authors recognise the difficulties in communicating specific symptoms to patients and, for example, the value of "word pictures" in describing symptoms. This is addressed by Shaw<sup>2</sup> in this supplement (see page iv25–iv27), and the workshop also identified the need for local definitions of specific symptoms, taking into account variations in the translation of words into other languages.

**Timescale and duration**

This is addressed elsewhere in the workshop report, and the actual timescale and duration measured will depend on the aims of the symptom assessment. However, timescale of symptom evaluation and/or duration of symptoms should always be clearly stated in any reporting of symptom assessment. For more discussion of the appropriate duration for assessment of symptom status, see McColl<sup>3</sup> in this supplement (page iv49–iv54).

**Use of response scales**

Response scales—for example, in the measurement of symptom severity—are frequently referred to as Likert scales,

and this term was used in workshop discussions. "Likert scale" is commonly used, for example, to describe symptom scales, such as "none, mild, moderate, severe". The original Likert scale (see Wyrwich and Staebler Tardino,<sup>4</sup> in this supplement (page iv45–iv48), for more on Likert scales) was a five point scale, from "strongly approve" to "strongly disapprove" with a defined ("no opinion") zero point. In other words, a strict definition of a Likert scale could include a neutral midpoint with the scale symmetrical about this point with positive and negative loadings. However, in practice, the issue of a zero midpoint (and thus an odd number of responses) comes down to the intention of the author, with arguments for and against the use of a neutral alternative. To accommodate this; while at the same time encompassing common usage of Likert scales, the term "modified Likert scale" is used throughout the workshop report.

## 1. DIAGNOSTIC USE OF SYMPTOMS: PROPOSITIONS, VOTING, DISCUSSION, AND COMMENTARY

### Introduction

Diagnostic symptom assessment is especially important in GORD where objective tests, such as endoscopy and oesophageal pH studies, are relatively insensitive. It is not enough however to document symptoms that may be important in GORD. Surveys suggest that approximately one third of the population experience heartburn,<sup>5</sup> and it is unlikely that all of these subjects have a disease. It is therefore important to determine the severity of symptoms and pathology that defines GORD. The next problem is establishing what symptom or symptoms are necessary for the diagnosis of GORD. Rome II focused on predominant heartburn as the feature that best identifies GORD, based on trial evidence that this group of patients with a normal endoscopy responds better to proton pump inhibitor (PPI) therapy than those with predominant dyspepsia or other symptoms.<sup>6</sup> It is important to establish the likely accuracy of this approach, how easy it is for patients to describe their predominant symptom, and what other features may enrich the diagnosis. This will be useful for clinicians diagnosing GORD and for identifying patients that are suitable for GORD trials.

The observation that the risk of subjects with severe reflux symptoms developing oesophageal adenocarcinoma was increased 40-fold<sup>7</sup> has raised the profile of GORD as a serious disease. The majority of patients with oesophageal adenocarcinoma have dysphagia as a symptom and most guidelines recommend that all patients with this symptom have urgent endoscopy. Dysphagia is also a common symptom of GORD and therefore the utility of investigating all patients with this problem needs to be questioned. These questions were addressed by the workshop under the following six topic headings:

- When does gastro-oesophageal reflux become GORD?
- What is the positive predictive value of predominant heartburn in diagnosing GORD?
- What is the negative predictive value of absence of predominant heartburn in excluding GORD?
- Does the practice setting in which the diagnostic assessment is made influence the positive predictive value of GORD symptoms?
- Are there any other symptoms that help make the diagnosis of GORD?
- What symptoms and characteristics identify reflux disease patients who are at relatively high risk of having or developing serious complications from this?

### Propositions, voting, and discussion

#### When does gastro-oesophageal reflux become GORD?

(1.1) GORD is defined by the presence of reflux oesophagitis (Los Angeles grades A–D) and/or when it causes reflux symptoms that are sufficient to impair quality of life and/or when it is associated with a risk of long term complications.

Strength of recommendation: agree strongly, 62%; agree, reservation, 27%; disagree, reservation, 12%; disagree strongly, 0%.

This is consistent with the definition of GORD in the Genval Workshop Report.<sup>8</sup> When symptoms significantly impact on patient quality of life, this fits with holistic definitions of disease. The question of what level of reflux symptom load impacts on quality of life is addressed in proposition 2.2. The workshop recommended that this should now be adopted as the working definition of GORD.

*Editorial comment.* "Risk of long term complications" includes any severity of mucosal breakage due to reflux oesophagitis, as well as stricture and development of Barrett's oesophagus. However, to clarify this, during the workshop, the definition was modified to include explicit mention of reflux oesophagitis, as defined by the Los Angeles classification system.<sup>9</sup> This is the final definition (above), which was strongly supported.

(1.2) In patients consulting with GORD, moderate symptoms and/or symptoms occurring two or more days per week significantly impair quality of life. (nature of evidence: B).

Strength of recommendation: agree strongly, 7%; agree, reservation, 63%; disagree, reservation, 30%; disagree strongly, 0%.

The question of the threshold level of symptoms that causes clinically relevant impairment of quality of life is influenced to some extent by how quality of life is measured, and evidence from studies in patients with more severe symptoms is limited by significant selection bias. The Genval report proposed that reflux disease is likely to be present when heartburn occurs on 2 or more days a week, on the basis of the negative impact of this symptom frequency on quality of life.<sup>8</sup> It was noted in the report however that the evidence at that time may have been insufficient to define severity of reflux induced symptoms by frequency alone. New data now support this hypothesis, with a marked fall in patients' willingness to accept two or more days of mild heartburn per week (fig 1). Over 90% of patients accepted up to one day of mild heartburn during treatment as sufficient control of their heartburn but this fell to 32% when they experienced mild heartburn on 2–4 days of the week.<sup>10</sup> These data seem to justify the "two or more days a week" cutoff for symptoms that impair quality of life. The concept that frequency of symptoms is correlated with severity is supported by new analyses of data from patients with

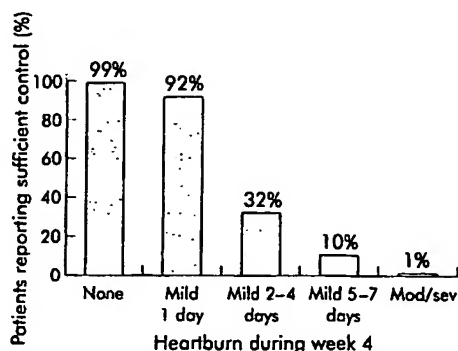


Figure 1 Most patients accept up to one day with mild heartburn per week during treatment. Few accept more frequent heartburn or moderate/severe heartburn.<sup>10</sup>

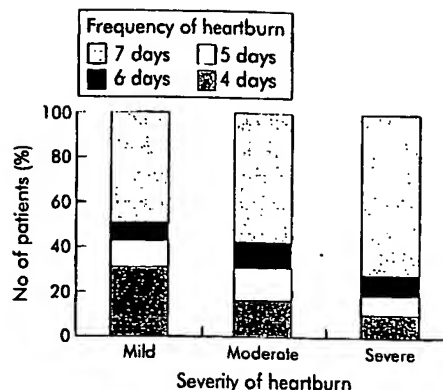


Figure 2 Patients with severe heartburn are likely to have more frequent heartburn than those with mild heartburn (AstraZeneca, data on file).

endoscopy negative GORD. These data show that patients with severe heartburn are more likely to experience daily heartburn than those with mild heartburn (fig 2) (AstraZeneca, data on file). Further support comes from the ProGERD study in over 5000 patients presenting with symptoms of GORD. In this study, both the SF-36 and QOLRAD scales show a decrease in quality of life dimensions with increasing frequency and severity of heartburn and, more particularly, indicate that the drop in quality of life is apparent when symptoms occur on more than one day of the week, or when they are of moderate or greater severity (AstraZeneca, data on file).

*Editorial comment.* While in general two or more symptoms per week is associated with impaired quality of life, clinical experience suggests there is the occasional patient that complains of infrequent but moderate or severe symptoms that are sufficiently troublesome to affect quality of life. It should also be noted that a minority of patients with more than twice weekly heartburn does not have impaired quality of life. This appears to be why 30% of workshop participants disagreed with the proposition.

#### What is the positive predictive value of predominant heartburn in diagnosing GORD?

(1.3) In at least 90% of people with heartburn as their sole symptom, this will be caused by gastro-oesophageal reflux (nature of evidence: D).

Strength of recommendation: agree strongly, 0%; agree, reservation, 17%; disagree, reservation, 35%; disagree strongly, 48%.

This proposition was rejected because only a very small subset of patients has a sole symptom, and there are no data available for such patients. In a study of patients with predominant heartburn whose GORD was defined by pH monitoring,<sup>11</sup> the specificity of heartburn was 89%, but sensitivity was 38%. Patient numbers were small, heartburn was not the sole symptom, and pH monitoring is not sufficiently accurate.

*Editorial comment.* There are propositions throughout this workshop that the group rejected or accepted where there was little or no evidence. This decision is therefore driven by clinical opinion and, for this proposition, the implication is that the group felt heartburn alone does not have a superior positive predictive value to heartburn as a predominant symptom, which is addressed in proposition 1.4.

(1.4) In at least 80% of patients consulting with heartburn as their predominant symptom, this is induced by gastro-oesophageal reflux (nature of evidence: C).



*Strength of recommendation: agree strongly, 37%; agree, reservation, 59%; disagree, reservation, 4%; disagree strongly, 0%.*

Acceptance of this proposition relied heavily on clinical experience, as there are no direct data to support it. Indirect data are available by extrapolation from studies of empirical PPI therapy and GORD diagnosis in patients with heartburn as their predominant symptom.<sup>12-15</sup> Sensitivity was 75–83% and specificity 55–63%. The Genval workshop concluded that when heartburn is a major or sole symptom, gastro-oesophageal reflux is the cause in at least 75% of individuals, and this was, again, based on consistency of indirect evidence and clinical experience.<sup>6</sup> It should be noted that the value of 80% accepted in the proposition here relates to patients consulting in secondary care with heartburn, and may be expected to be lower in people with heartburn in the general population.

**(1.5) Heartburn is associated with epigastric pain in at least two thirds of patients with upper gastrointestinal symptoms (nature of evidence: C).**

*Strength of recommendation: agree strongly, 4%; agree, reservation, 62%; disagree, reservation, 15%; disagree strongly, 19%.*

The quite wide scatter of votes reflects the lack of studies of adequate design which specifically address the proposition, the fact that the relevant data available are largely secondary unpublished analyses, and that the definition, frequency, and severity scorings of heartburn and epigastric pain are generally not reported in detail. Consequently, there was debate over the precise proportion of patients with both symptoms. Support for the proposition comes from unselected subjects surveyed randomly in UK general practices.<sup>16</sup> Re-analysis of these data indicate that of the 3177/8350 individuals (38%) that had upper gastrointestinal symptoms, 2403/3177 (76%) had heartburn more than once per month, and 1518/2403 (63%) of these individuals had coexisting epigastric pain. The Canadian Cadet-PE study in patients with uninvestigated dyspepsia also supports the proposition. Of 84% of patients with upper gastrointestinal symptoms found to have heartburn or regurgitation, 75% also had ulcer-like dyspepsia (AstraZeneca, data on file). Reanalysis of the AstraZeneca database from a study comparing healing of reflux oesophagitis with esomeprazole and lansoprazole in over 5000 patients in the USA with reflux oesophagitis and heartburn<sup>17</sup> shows that 66% of these patients also had epigastric pain at baseline. In general practice in Denmark,<sup>18</sup> 32% of consecutive consulting dyspepsia patients had dominant heartburn and/or regurgitation, 37% had dominant epigastric pain, and 66% had both. In conclusion, the available data indicate that there is significant overlap between heartburn and epigastric pain, but controversy remains over the precise extent of this overlap.

**(1.6) The epigastric pain that occurs in patients with reflux disease is generated predominantly by oesophageal contact with refluxate (nature of evidence: B).**

*Strength of recommendation: agree strongly, 4%; agree, reservation, 46%; disagree, reservation, 42%; disagree strongly, 8%.*

The evenly split vote reflects the absence of data showing a temporal association between epigastric pain and reflux episodes. Evidence to support the proposition is limited and circumstantial. Epigastric pain is part of the symptom complex for many GORD patients, and improves with PPI therapy, although to a lesser extent than heartburn. Some functional dyspepsia patients with non-dominant heartburn have increased oesophageal acid exposure<sup>19</sup> but there are no prospective data to show that epigastric pain in GORD is triggered predominantly by gastro-oesophageal reflux. A single study has shown an association between oesophageal acidification by acid perfusion and epigastric pain, although this was in duodenal ulcer patients.<sup>20</sup>

**(1.7) Patients with heartburn and epigastric pain find it difficult to describe their predominant symptom (nature of evidence: C).**

*Strength of recommendation: agree strongly, 21%; agree, reservation, 71%; disagree, reservation, 8%; disagree strongly, 0%.*

No studies have directly addressed this although it is supported by indirect evidence.<sup>11 21-23</sup> Epigastric pain and heartburn frequently coexist in various populations with dyspepsia, and a significant proportion cannot select their predominant symptom. When primary care patients with dyspepsia were asked to select their predominant symptom from heartburn, regurgitation, or epigastric pain, 19% were unable to choose, 10% said that it was none of these, and 10% failed to respond.<sup>21</sup> This highlights two elements to the question: firstly, the patient's ability to differentiate epigastric pain from heartburn and, secondly, their ability to select a predominant symptom.

**(1.8) A word description helps patients decide whether heartburn or epigastric pain is the predominant symptom (nature of evidence: C).**

*Strength of recommendation: agree strongly, 17%; agree, reservation, 75%; disagree, reservation, 8%; disagree strongly, 0%.*

Evidence to support this comes from two studies that have documented the value of using word descriptions for heartburn that included upward movement of pain, discomfort, or a burning feeling starting in the epigastrium and rising towards the neck.<sup>24 25</sup>

*Editorial comment.* Phrasing of the word picture is important because if more than two concepts are combined in the same sentence this can be confusing for respondents.<sup>21</sup>

**What is the negative predictive value of absence of predominant heartburn in excluding GORD?**

**(1.9) In people with upper abdominal pain in whom heartburn occurs as a secondary symptom, GORD is present in approximately 30% (nature of evidence: C).**

*Strength of recommendation: agree strongly, 15%; agree, reservation, 70%; disagree, reservation, 10%; disagree strongly, 5%.*

Direct evidence is not available for the significance of heartburn as a secondary (that is, non-dominant) symptom. Using likelihood ratios on the available data,<sup>26</sup> the probability of GORD in the absence of predominant heartburn can be estimated to be 12%,<sup>27</sup> 30%,<sup>28</sup> and 34%,<sup>11</sup> based on 50% probability of having GORD in all patients attending a secondary care dyspepsia clinic. A study of patients with a primary symptom of dyspepsia and secondary heartburn suggests that at least 13% of patients had endoscopically confirmed reflux oesophagitis.<sup>29</sup> Assuming that patients with GORD have oesophagitis or endoscopy negative reflux disease in roughly equal proportions, then these data also support a value of 25–30% as an approximate estimate.

**Does the practice setting in which the diagnostic assessment is made influence the positive predictive value of GORD symptoms?**

**(1.10) Of patients who seek advice in primary care about predominant heartburn, less than 70% will have reflux disease (nature of evidence: B).**

*Strength of recommendation: agree strongly, 0%; agree, reservation, 52%; disagree, reservation, 32%; disagree strongly, 16%.*

Data in primary care on this proposition are lacking, and the lack of direct evidence is compounded by variation in how reflux disease is defined, with most data based on endoscopic detection of oesophagitis, on pH monitoring, or response to PPI therapy. Additionally, the term "heartburn" is not used consistently in different settings.

*Editorial comment.* The majority felt that the prevalence of GORD was likely to be lower in the primary care setting than



in a secondary care dyspepsia clinic. The positive predictive value of predominant heartburn will therefore also fall compared with that seen in secondary care studies. The value of 70% is not supported by direct data and is estimated using likelihood ratios and extrapolating from secondary care studies.<sup>26</sup>

Looking at the propositions above collectively raises some questions. The workshop participants agreed that in at least 80% of patients consulting with heartburn as their predominant symptom, this is induced by GORD (proposition 1.4). However, there is significant overlap between heartburn and epigastric pain (proposition 1.5), and participants agreed that patients with heartburn and epigastric pain find it difficult to describe their predominant symptom (proposition 1.7), although this can be helped by use of a word description (proposition 1.8). Opinion was divided on the proposition above (proposition 1.10) that of patients who seek advice in primary care about predominant heartburn, less than 70% will have reflux disease. The responses to these propositions raise the issue as to from what perspective "predominant" heartburn is defined. Is a patient's self-reporting of heartburn as the predominant symptom adequate, or are appropriately trained clinicians more accurate? To help clarify this, a further proposition (proposition 1.11) was developed during the plenary session, which seeks to define predominant heartburn.

**(1.11) Predominant heartburn is defined as the most bothersome symptom based on a physician interview.**

*Strength of recommendation:* agree strongly, 31%; agree, reservation, 58%; disagree, reservation, 12%; disagree strongly, 0%.

Taken together with propositions 3.13 and 3.14, a key recommendation from the workshop is that global clinical opinion, based on a technically adequate clinician interview, is the most accurate approach to the diagnosis of GORD, rather than relying on the patient's description of their predominant symptom. The positive predictive value of the symptom of predominant heartburn to detect GORD will still fall as the prevalence of GORD falls, even if a trained clinician assesses symptoms.

**(1.12) Less than 50% of people found to have heartburn of any severity by a population survey will have reflux disease (nature of evidence: E).**

*Strength of recommendation:* agree strongly, 4%; agree, reservation, 75%; disagree, reservation, 17%; disagree strongly, 4%.

There are few primary data to support this hypothesis and this is compounded by a lack of a gold standard test to diagnose GORD. It was felt that the prevalence of GORD was likely to be lower than seen in either primary or secondary care and that the positive predictive value of heartburn (particularly of any severity) will fall.

*Editorial comment.* The implication of this proposition is that population surveys reporting the prevalence of "heartburn" in a general population may not be identifying GORD as accurately as studies in secondary care patient populations. This does not invalidate these studies but suggests the results should be interpreted with caution. Many people may report having heartburn but it may not be related to gastro-oesophageal reflux or if it is, it may not reach the threshold of severity required to define "disease".

**Are there any other symptoms that help make the diagnosis of GORD?**

**(1.13) In people with predominant heartburn, this is more likely to be due to gastro-oesophageal reflux if regurgitation has also been noted (nature of evidence: D).**

*Strength of recommendation:* agree strongly, 13%; agree, reservation, 35%; disagree, reservation, 52%; disagree strongly, 0%.

The even split in the vote reflects the paucity of studies in this area. Acceptance was based on clinical experience, while disagreement was due to a lack of evidence. A single study has reported the positive predictive value of symptoms versus pH testing in patients with symptoms suggestive of reflux disease.<sup>27</sup> The positive predictive value of heartburn was 59%, rising slightly to 66% when regurgitation was also present, although it was also 66% for regurgitation alone. Similarly, the positive predictive values were 70% for both heartburn and regurgitation using oesophageal pH monitoring as the reference diagnostic test in patients with suspected reflux disease although this study does not provide data on the value of heartburn and regurgitation together.<sup>28</sup> Consideration of this question is confounded by the need for a universal definition of regurgitation, and there are anecdotal reports that interpretation of the term may not be the same in different languages. This may be enhanced by use of a word description, as is the case for more reliable recognition of heartburn.

*Editorial comment.* The uncertainty in this and other related questions emphasises the need for high quality, prospective, cross sectional surveys that carefully detail patients' symptoms and correlate this with the final diagnosis reached.

**(1.14) Occurrence of reflux symptoms for more than six months is a confirmatory feature of GORD (nature of evidence: E).**

*Strength of recommendation:* agree strongly, 17%; agree, reservation, 61%; disagree, reservation, 17%; disagree strongly, 4%.

Although there are no direct data to support duration of symptoms as being helpful in the diagnosis of GORD, acceptance by the majority of participants was based on the view that it makes clinical sense. Most clinical trials report the duration of GORD symptoms in terms of years rather than months, which is not helpful in assessing the proposition.

*Editorial comment.* Two case control studies have shown that increasing duration of reflux symptoms increases the risk of developing oesophageal adenocarcinoma.<sup>29</sup> This was taken as very indirect evidence supporting the proposition, under the assumption that part of the reason for this may be that chronic symptoms are more likely to be due to more severe GORD. Additionally, although no studies have directly addressed the proposition, it is in accordance with patients' experience, with most reporting symptoms for six months or more. The strength and consistency of the supporting evidence is probably underestimated.

**(1.15) In approximately 30% of patients with recurrent non-cardiac chest pain, this is caused by gastro-oesophageal reflux (nature of evidence: B).**

*Strength of recommendation:* agree strongly, 21%; agree, reservation, 75%; disagree, reservation, 4%; disagree strongly, 0%.

Recurrent angina-like chest pain is a symptom of GORD although GORD and chest pain are linked through intermediary mechanisms that interfere with establishing a cause-effect relationship. However, there was broad acceptance of gastro-oesophageal reflux as a cause of non-cardiac chest pain, and debate centred around the proportion of patients in which this is the case. Updating an analysis of cross sectional surveys in patients with non-cardiac chest pain<sup>31</sup> with two subsequent studies<sup>32,33</sup> shows that 200/947 non-cardiac chest pain patients (21%—from 14 studies) had endoscopically confirmed oesophagitis, 423/1002 (42%—from 14 studies) had abnormal acid exposure time, and 278/787 (39%—from 16 studies) had a positive association of chest pain with reflux episodes during pH monitoring. Evidence for an association between non-cardiac chest pain and GORD also comes from studies of the response of non-cardiac chest pain

to PPI therapy<sup>33-35</sup> and laparoscopic surgery,<sup>36</sup> although the size of response varies between studies. The available data indicate that the prevalence of reflux induced, provoked, or otherwise related pain in the non-cardiac chest pain population is substantial, possibly representing 30–50% of patients.

*Editorial comment.* A label of non-cardiac chest pain suggests the patient has had extensive cardiac investigations to exclude ischaemic heart disease. These patients, by definition therefore, are highly selected and there is likely to be further bias in those patients that are included in studies. While selection bias would lead to an overestimate of the proportion of patients in which GORD is the cause of non-cardiac chest pain, the data are likely to be valid for patients attending secondary care clinics.

What symptoms and characteristics identify reflux disease patients who are at relatively high risk of having or developing serious complications from this?

(1.16) *Presence of dysphagia of any pattern should not be considered an alarm symptom* (nature of evidence: C).

*Strength of recommendation:* agree strongly, 8%; agree, reservation, 31%; disagree, reservation, 15%; disagree strongly, 46%.

The particularly broad spread in voting highlights differences in interpretation of how to act on dysphagia of any severity, duration, or pattern of occurrence given the loose definitions of dysphagia used in the community. Some 78% of oesophageal cancer cases have dysphagia<sup>37</sup> but conversely, dysphagia is common in the community. A pooled analysis of six community surveys<sup>16, 27, 32, 38-40</sup> done for the purpose of this workshop, involving 12 700 subjects, indicates a point prevalence of dysphagia in the community of 14%. Dysphagia is particularly common in patients with heartburn, increasing in incidence with increasing frequency of heartburn. In five large randomised controlled esomeprazole trials, involving approximately 12 000 reflux oesophagitis patients, 37% had dysphagia but there were no cases of oesophageal malignancy.<sup>41</sup> Thus while dysphagia, when correctly evaluated, may indicate a risk of oesophageal malignancy (see the next proposition, 1.17), its presence per se may not necessarily be regarded as an alarm symptom.

*Editorial comment.* The voting reflects concern that physicians may be too dismissive of dysphagia, and not sufficiently diligent regarding the duration and pattern of the symptom to decide whether or not it is an alarm symptom (see the next proposition 1.17). There is also a lack of consensus on how to elicit a symptom of dysphagia and how to assess its severity in clinical practice or research. When a patient reports dysphagia, either spontaneously or in response to a direct question from the physician, the physician should then go through a number of steps to filter those that require investigation. In other words, given the high level of self-reporting of dysphagia, it is appropriate that dysphagia of any pattern should not be considered an alarm symptom. Despite the vote of the workshop, the editorial group for the report believe that it is not appropriate to endoscope everyone who reports dysphagia, as it is very common, responds rapidly to treatment, and is not associated with a level of risk to justify screening. Lack of adequately researched evidence on how to identify patients in whom dysphagia is of concern warrants study but conventional clinical wisdom is that in patients with newly appearing dysphagia, increasing severity of this symptom, or persistence of dysphagia despite therapy, this demands investigation.

(1.17) *Dysphagia is a useful indicator of risk for oesophageal malignancy, provided its duration and pattern of occurrence are also evaluated* (nature of evidence: D).

*Strength of recommendation:* agree strongly, 21%; agree, reservation, 71%; disagree, reservation, 8%; disagree strongly, 0%.

Broad acceptance of this puts the previous proposition in perspective. Three cross-sectional surveys have evaluated the role of dysphagia as an alarm symptom, and although they have limitations, the data indicate that dysphagia is not a good predictor of the presence of cancer.<sup>42-45</sup> Despite this lack of evidence, and although there are no reports detailing the impact of dysphagia pattern and duration on risk of cancer, the proposition was accepted on the grounds of clinical experience. This assumes that the time of onset, progression, and associated features, such as weight loss and family history, are evaluated.

(1.18) *Patients with reflux disease for more than five years are at an increased risk of long segment Barrett's oesophagus compared with a control population* (nature of evidence: C).

*Strength of recommendation:* agree strongly, 13%; agree, reservation, 71%; disagree, reservation, 17%; disagree strongly, 0%.

The ideal study to support this proposition has not been done. Indirect supportive evidence comes from studies in patients with reflux symptoms and frequent antacid users,<sup>46-49</sup> and from studies reporting long duration of symptoms to be a risk factor for Barrett's oesophagus.<sup>30, 51</sup> These data do not specifically highlight the five year timeframe but do suggest Barrett's oesophagus is associated with chronic reflux symptoms.

(1.19) *People who have had heartburn severe enough to be defined as causing reflux disease for more than five years are at an increased risk of oesophageal adenocarcinoma compared with a control population* (nature of evidence: B).

*Strength of recommendation:* agree strongly, 37%; agree, reservation, 56%; disagree, reservation, 7%; disagree strongly, 0%.

Three case control studies have demonstrated an association between oesophageal adenocarcinoma and increasing duration of GORD symptoms,<sup>7, 30, 52</sup> as well as increasing frequency of symptoms.<sup>7, 52</sup> One study<sup>7</sup> used squamous oesophageal cancers as a second control group, so recall bias is unlikely to explain the association.

(1.20) *Classical Barrett's oesophagus is present in less than 1% of reflux disease patients younger than 50 years of age* (nature of evidence: C).

*Strength of recommendation:* agree strongly, 12%; agree, reservation, 76%; disagree, reservation, 12%; disagree strongly, 0%.

"Classical" indicates long segment Barrett's oesophagus that is at least 3 cm in length. Supportive data for the proposition are limited. A prevalence of Barrett's oesophagus of 5% has been reported in patients aged 40–49 years, rising to 10% in those aged 50–69 years, although the study population of relatives of patients with Barrett's oesophagus was highly selected.<sup>53</sup> Data from patients in the Mayo Clinic between 1976 and 1989 indicate that the prevalence of Barrett's oesophagus is 0.41% in patients aged 30–49 years and 1.61% in those aged 50–69 years.<sup>53</sup>

*Editorial comment.* The implication from the voting on this proposition is that young patients with reflux symptoms do not need endoscopy to exclude Barrett's oesophagus. It must be noted however that most of the data is from all patients endoscoped rather than patients specifically with reflux disease.

(1.21) *Of patients with oesophageal adenocarcinoma in developed countries, more than 95% are older than 50 years of age.* (nature of evidence: A).

*Strength of recommendation:* agree strongly, 92%; agree, reservation, 8%; disagree, reservation, 0%; disagree strongly, 0%.

There is geographical variation in the prevalence of oesophageal carcinoma but published data strongly support the proposition.<sup>54-60</sup>

(1.22) *Compared to females, males with Barrett's oesophagus have greater than twice the risk of developing adenocarcinoma* (nature of evidence: B).

Strength of recommendation: agree strongly, 48%; agree, reservation, 52%; disagree, reservation, 0%; disagree strongly, 0%.

There is clear evidence to support this<sup>54, 61-64</sup> although there are caveats to the interpretation of the epidemiology of oesophageal adenocarcinoma. There are some uncertainties about the nature of adenocarcinoma of the gastro-oesophageal junction. Some reports combine junctional and oesophageal body cancer, and coding conventions for junctional and oesophageal adenocarcinoma were altered in the 1990s.<sup>60, 65</sup> The proposition relates to Barrett's oesophagus although it may understate the differential in risk between males and females in so far as the differential is probably greater for adenocarcinoma per se, and most cases of adenocarcinoma are not preceded by Barrett's oesophagus diagnosed at endoscopy.

(1.23) *Among patients over 50 years of age in primary care presenting with reflux symptoms for over five years, the yield of endoscopy in any year for detecting oesophageal adenocarcinoma is less than 1 in 1000* (nature of evidence: B).

Strength of recommendation: agree strongly, 46%; agree, reservation, 50%; disagree, reservation, 4%; disagree strongly, 0%.

This is supported by publications reporting a risk of oesophageal adenocarcinoma in Barrett's oesophagus of approximately 0.5% per annum,<sup>66</sup> coupled with a prevalence of Barrett's oesophagus in patients with reflux symptoms of approximately 10%. The data are limited by differing definitions of Barrett's oesophagus, inclusion and exclusion of short segment Barrett's oesophagus, and different definitions of landmark features, such as the gastro-oesophageal junction. A prevalence of long segment Barrett's of 7% was seen in one study of asymptomatic patients attending colorectal cancer screening but this was a study in US veterans and was not felt to be generalisable.<sup>67</sup>

### Future directions for research

Statistical techniques have been developed that overcome many of the problems of not having a gold standard to diagnose reflux disease. Future studies should use these techniques to assess the accuracy of heartburn to diagnose GORD in secondary and primary care populations. A comprehensive history should be taken in these studies so that the additional value of regurgitation and duration of symptoms can be evaluated as well as assessing the overlap with epigastric pain.

Most guidelines recommend that patients with dysphagia should have endoscopy. This would entail endoscopic 14% of the entire population given the high prevalences of reflux disease and dysphagia. Direct assessment of the additional value of the duration and pattern of occurrence of dysphagia would be helpful in refining our perception of dysphagia and risk of neoplasia.

The risk of Barrett's oesophagus and oesophageal adenocarcinoma with increasing duration and severity of heartburn has now become established but this important finding is based on only a few studies. Further studies evaluating these associations in different populations would therefore be useful.

## 2. ASSESSMENT OF REFLUX SYMPTOM SEVERITY: PROPOSITIONS, VOTING, DISCUSSION, AND COMMENTARY

### Introduction

Translation of the results of clinical research studies into clinical practice is a significant challenge. For the patient presenting in clinical practice, several questions need to be addressed in order to determine optimal therapy. Are

symptoms reflux related and, if so, are they typical or atypical? Are symptoms mild or severe, and are they associated with reduced quality of life or oesophageal damage? If treatment is warranted, will it be effective in the short and long term? Should the response to treatment be complete or satisfactory to the patient? These may not be the same thing and, furthermore, it is not clear that the measure of response should be equivalent for all symptoms.

For initial therapy, there are two major strategies—start high with daily PPI or at a lower level with daily H<sub>2</sub> receptor antagonists. Experience with testing these options in the CADET-HR study underlines the difficulties of translating outcomes from clinical trials such as this into clinical practice. The different measures of symptom response used in this study gave different estimates of the extent of the superiority of omeprazole over ranitidine.<sup>68</sup> Greatest differentiation was seen if absence of reflux induced symptoms was used but the absolute response rate was lower.

The same uncertainties about the most relevant outcome measures also apply to the evaluation of reflux symptom relapse during long term management. For instance, the CADET-HR study found that the number of heartburn free days gave the greatest differentiation between on-demand omeprazole or ranitidine therapy compared with slightly different versions of "unwillingness to continue".<sup>69</sup>

Data such as these underline the difficulties experienced when translating the results of clinical trials into clinical practice, and the need for guidance when assessing reflux symptom severity. However, identification of these difficulties raises many questions. For example, should it be symptom severity, duration, frequency, or "density" that is assessed? Should the response to therapy be documented as complete abolition of symptoms or adequate control of symptoms, and should the response be assessed by the clinician or by the patient? Is heartburn the only symptom that should be assessed and, if not, what other symptoms are relevant? These and other issues were addressed in this session of the workshop, and the outcome of the deliberations will be presented under five topic categories.

- How should treatment response be measured in reflux disease?
- Which of the typical reflux symptoms should be measured to assess treatment response?
- What are the outcome variables for long term therapy?
- Are there symptom patterns that predict outcome for therapy of reflux disease?
- How should extra-oesophageal symptoms, ascribed to reflux, be monitored during therapy?

### Propositions, voting, and discussion

How should treatment response be measured in reflux disease?

(2.1) *In clinical trials, the proportion of patients who have been free of heartburn for one week prior to assessment is the optimal end point for assessment of symptom response* (nature of evidence: B).

Strength of recommendation: agree strongly, 22%; agree, reservation, 44%; disagree, reservation, 33%; disagree strongly, 0%.

Placebo controlled clinical trials of antisecretory therapy in patients with endoscopy negative GORD have shown that the differential between active treatment and placebo increases from an end point of "did study medication give sufficient control of your symptoms",<sup>70, 71</sup> to "adequate control of heartburn (one day with episodes of mild heartburn in the last seven days)",<sup>70, 71</sup> to "absence of heartburn at four weeks (no heartburn in the last seven days)".<sup>70, 71</sup> In other words,

the placebo response decreased with increasing stringency of the end point.

However, because more than 90% of patients accept up to one day of mild heartburn during treatment as sufficient control of their heartburn (see fig 1),<sup>6</sup> a significant number of workshop participants voted to "disagree with the proposition with reservation". Counter to this, it was noted that in the USA at least, patients are willing to pay more for absence of symptoms,<sup>73</sup> suggesting that classification of a response as sufficient does not mean that patients do not want, or should be denied, more effective therapy.

This poses a fundamental question: should the end point in clinical trials be optimal for the patient or, for example, optimal for discriminating between treatments? The majority view was that what patients accept is not necessarily optimal as a clinical trial end point, in part because acceptance may depend on other factors in addition to the frequency and severity of symptoms. It was felt that an end point, defined as "no episodes of heartburn during the last seven days of study" is attractive as it is rigorous, unambiguous and, therefore, methodologically sound. A one week timeframe was considered to be reasonable for standard clinical study durations although it may not be appropriate for shorter studies intended, for example, to assess the rapidity of symptom improvement. The advantages of using a one week timeframe for an end point are that it results in low placebo response rates and that it provides the patient with an internal standard of the best possible care. In addition, an end point of complete absence of heartburn at four weeks predicted healing in patients with reflux oesophagitis,<sup>74-75</sup> and predicts subsequent symptom status while on PPI therapy.<sup>76</sup>

**Editorial comment.** In clinical trials, complete absence of symptoms for a predefined time period provides a clear reproducible end point that allows comparison between studies. There were however concerns that this end point is too stringent and too far removed from clinical practice. Consequent discussion in the workshop identified that a less stringent end point (for example, less than two mild symptom episodes in the prior week) may be an acceptable measure of symptom response in clinical practice.

The discussion of this proposition did not address a precise definition of "absence of symptoms" but it is worth noting that terms used in recent oesophagitis healing studies,<sup>17-24</sup> "complete resolution of heartburn" (investigator assessment of symptoms over the previous week) and "sustained resolution of heartburn" (patient diary card record of symptoms on the previous seven days), led to somewhat different estimates of treatment efficacy within the same studies. Both measures are consistent with the above proposition and, although the difference in reported outcome may reflect discrepancies arising from patient self-assessment compared with investigator assessment (discussed in proposition 2.8, below), it is necessary to ensure that all clinical trial end points are defined as precisely as possible.

**(2.2) In clinical practice, patient satisfaction with improvement in reflux symptoms is the optimal measure of response to therapy** (nature of evidence: D).

**Strength of recommendation:** agree strongly, 8%; agree, reservation, 32%; disagree, reservation, 32%; disagree strongly, 28%.

Patient satisfaction with improvement in reflux symptoms was seen to be an intuitively meaningful measure of treatment response. However, the very limited relevant data available from clinical practice indicate that there may be little difference in patient satisfaction with respect to the extent of symptom reduction (see section 4). Additionally, there are measurement issues with the data available, such as use of single item measures, response bias, and acquiescence bias. The majority of participants therefore questioned

whether patient satisfaction with improvement in reflux symptoms has actually been shown to be the optimal measure, especially given the lack of validated tools for measurement of satisfaction. In addition, a confounding factor is that patient satisfaction is related to their expectations prior to therapy. The challenges associated with measurement of patient expectation and satisfaction are addressed in more detail in a later section.

**(2.3) In clinical practice, assessment of symptom response using daily diaries is feasible** (nature of evidence: C).

**Strength of recommendation:** agree strongly, 8%; agree, reservation, 0%; disagree, reservation, 12%; disagree strongly, 81%.

**(2.4) In clinical practice, it is useful to assess symptom response with daily diaries** (nature of evidence: C).

**Strength of recommendation:** agree strongly, 8%; agree, reservation, 4%; disagree, reservation, 23%; disagree strongly, 65%.

Although the value of daily diaries was recognised in the workshop, their use was not considered to be practicable in clinical practice. Daily diaries have been used extensively in the clinical trial setting, providing valuable data and high diary response rates have been reported (see McColl<sup>3</sup> in this supplement (page iv49-iv54)). In clinical practice however, accuracy and compliance are likely to be poor. Diary card records of peak flow measurements by asthma patients have been reported to contain at least one discrepancy in 75% of cases<sup>77</sup> although this may reflect poor compliance with the process of completing a daily diary. In addition, actual compliance with paper diaries has been shown to be only 11% compared with the 90% compliance that was reported by patients, and "hoarding" (when the patient fills in the diary at the end of the week, for example) was common, although the study which generated these data employed a rigorous protocol, requiring four diary entries per day.<sup>78</sup> Actual compliance was 94% when electronic diaries were used but this is not currently practicable for broad use in clinical practice. While the use of daily diaries in clinical practice was not seen to be practicable, the second proposal was not rejected as strongly.

**Editorial comment.** This discussion reflects the view that daily diaries may still be qualitatively useful in clinical practice in helping assess efficacy of therapy in selected patients, and as a tool to facilitate clinician/patient communication. (See also McColl<sup>3</sup> in this supplement (page iv49-iv54) for discussion of diary cards.)

**(2.5) In clinical trials, a modified Likert scale is superior to a visual analogue scale for measurement of symptom status** (nature of evidence: C).

**Strength of recommendation:** agree strongly, 31%; agree, reservation, 65%; disagree, reservation, 4%; disagree strongly, 0%.

Comparison of modified Likert scales and visual analogue scales (VAS) has shown that it is time consuming to train patients to use a VAS, and that it makes more sense to patients to discuss changes on a 1-7 point modified Likert scale than in terms of a 10-20 mm change on a 100 mm VAS.<sup>79-81</sup> A VAS is also more difficult to complete for the illiterate and the elderly.<sup>82-81</sup>

**Editorial comment.** The level of evidence was perhaps underestimated in the discussion. A detailed review of the literature (see also Wyrwich and Staebler Tardino,<sup>4</sup> in this supplement (page iv45-iv48), for discussion of VAS versus modified Likert scales) suggests that there is reasonable evidence to support the proposition.

**(2.6) In clinical trials, seven is the optimal number of response options in a modified Likert scale for measurement of symptom status** (nature of evidence: C).

*Strength of recommendation: agree strongly, 30%; agree, reservation, 63%; disagree, reservation, 7%; disagree strongly, 0%.*

A seven point adjectival scale allows identification of small but clinically relevant changes and is suitable from a psychometric point of view. A change of 0.5 points on a seven point scale has been shown to be clinically relevant in GORD using the gastrointestinal symptoms rating scale (GSRS) reflux dimension.<sup>82</sup> Five point scales were discussed as a simpler alternative<sup>83</sup> but these have not been validated in GORD, and have the drawback that more patients are likely to choose the midpoint than with a seven point scale. Seven point scales are probably optimal but they need more extensive validation in reflux disease, particularly when translated into other languages.

*Editorial comment.* Taking propositions 2.5 and 2.6 together, the conclusion is that validated outcome measures with established responsiveness should be applied in clinical trials, and moreover that a seven point modified Likert scale should be used to assess symptom outcomes, rather than dichotomous "yes/no" scales, other scale gradings, or VAS. Most clinical trials to date have used four point scales, which is probably suboptimal.

**(2.7) In clinical trials, a symptom improvement score of 0.5 on a seven point modified Likert scale over placebo is the minimally important difference (nature of evidence: C).**

*Strength of recommendation: agree strongly, 0%; agree, reservation, 23%; disagree, reservation, 46%; disagree strongly, 31%.*

There are limited data to support the proposition as it relates to global symptom improvement but existing data support the notion that a change of 0.5 is a minimal clinically important difference with respect to the reflux dimension of the GSRS. Furthermore, there are data to support an improvement score of 0.5 on a seven point modified Likert scale as a minimally important difference using specific quality of life scales. Mean changes in the QOLRAD scale have been shown to correlate with overall treatment effect classifications, according to a seven point modified Likert scale.<sup>82</sup>

*Editorial comment.* The level of evidence is probably underestimated in that the cited studies do provide evidence in support of the clinical relevance of an improvement of 0.5 points. However, despite initial validation studies,<sup>84</sup> data are not available to confirm that a change of this magnitude is a minimal clinically important difference for global symptom scales.

**(2.8) Patient self-report of reflux symptoms is more appropriate than clinician assessment in measuring treatment effect (nature of evidence: C).**

*Strength of recommendation: agree strongly, 44%; agree, reservation, 41%; disagree, reservation, 11%; disagree strongly, 4%.*

In general, there is only weak correlation between patient and clinician assessment of symptom severity.<sup>85</sup> Analysis of the AstraZeneca clinical trial database in GORD<sup>86</sup> shows fair to moderate agreement between investigators and patients, with better agreement at the lower end of the symptom severity continuum. However, clinicians tended to underestimate symptom severity and, although this may be partially due to interpretation of heartburn, the same pattern was seen across the range of GORD symptoms and has been reported generally for other conditions.<sup>85</sup> As it is the patient, not the clinician, who experiences symptoms, it was agreed that more weight should be assigned to the patient's assessment. This proposition relates only to the assessment of symptom severity and treatment effect for defined symptoms. The assessment of symptoms for diagnostic purposes may require greater input from the clinician.

*Editorial comment.* See McColl<sup>3</sup> in this supplement (page iv49–iv54) for a more detailed discussion of clinician versus patient assessments. The recommendation that self-reported measures of reflux symptoms are preferable to physician based measurement in clinical trials is an important concept. It reflects the reality that the physician's assessment is, of necessity, based on the patient's self assessment and that there is, therefore, no a priori reason to accept the physician's assessment preferentially. However, this recommendation is distinct from the recommendation that global clinical opinion, based on a technically adequate clinician interview, is the most accurate approach to the diagnosis of GORD (see propositions 1.11, 3.14, and 3.13). Diagnosis is more complex (see proposition 1.11 which specifies the physician interview as the means of diagnosing predominant heartburn) than assessment of therapy. While patients may find it difficult to describe or define their predominant symptom (see proposition 1.7), self-reporting of symptoms following therapy is much simpler, as it involves a predefined symptom scale or a dichotomous "yes/no" response and a baseline comparator.

**(2.9) Measurement of heartburn severity does not provide any additional information to the measurement of heartburn frequency in assessing response to therapy (nature of evidence: C).**

*Strength of recommendation: agree strongly, 0%; agree, reservation, 8%; disagree, reservation, 46%; disagree strongly, 46%.*

Both symptom frequency and severity are important in assessing response to therapy. An analysis by Sharma and colleagues<sup>1</sup> in this supplement (page iv58–iv65), indicates that frequency is a more sensitive and conservative measure than severity of symptoms but that severity correlates better with healing of oesophagitis, although the data are sparse. Measurement of frequency of heartburn alone risks underestimating the impact on the patient of infrequent but severe episodes exemplified by nocturnal heartburn with choking or severe non-cardiac chest pain. Given that more than one episode of mild heartburn per week is not acceptable to patients (see fig 1), both severity and frequency are important to the patient.

*Editorial comment.* It is important to emphasise that this proposition addressed the relationship between symptom characteristics and the response of symptoms to treatment. It did not address the relationship between symptom characteristics and the presence or persistence of oesophagitis in response to therapy.

**(2.10) Both frequency and severity of heartburn should be measured on therapy, using validated scales, in clinical trials where heartburn is the primary entry criterion.**

*Strength of recommendation: agree strongly, 59%; agree, reservation, 37%; disagree, reservation, 4%; disagree strongly, 0%.*

*Editorial comment.* Acceptance of this proposition is a corollary of the rejection of the previous proposition. As frequency and severity may vary independently in some, if not all, patients, it is important to measure changes in both when assessing a patient's response to therapy.

**Which of the typical reflux symptoms should be measured to assess treatment response?**

**(2.11) In clinical trials, there is no need to monitor all reflux symptoms in patients with typical symptoms since heartburn response is associated with response of other symptoms (nature of evidence: C).**

*Strength of recommendation: agree strongly, 4%; agree, reservation, 19%; disagree, reservation, 63%; disagree strongly, 15%.*

An analysis by Sharma and colleagues<sup>1</sup> in this supplement (see page iv58–iv65) indicates that absence of heartburn correlates with absence of regurgitation, and with



absence of dysphagia. However, this is based on patient groups, and it is not known if this applies in individual patients. Indeed, the severity of regurgitation and heartburn does not correlate in all patients. Different reflux related non-heartburn symptoms may be present in different patients. For example, in a recent study, acid regurgitation (72.6%) was significantly more prevalent than epigastric pain (50.0%), retrosternal pain (47.1%), retrosternal tightness (33.2%), or nausea (36.5%), and these symptoms responded differently to therapy.<sup>85</sup> Thus monitoring heartburn alone risks missing improvement or worsening of other symptoms attributable either to the disease process or to therapy.

**Editorial comment.** Symptoms other than heartburn should be monitored in clinical trials. One difficulty is that although patients may have reflux symptoms other than heartburn, it is heartburn that is the enrolment criterion for most studies of therapy in GORD, and change in heartburn severity or frequency is the primary symptomatic outcome. Thus studies are not generally designed or powered to examine the effect of therapy on other symptoms or to correlate changes in heartburn with changes in other symptoms. In addition, most data are from acid suppression trials in which regurgitation and dysphagia both respond to therapy. However, symptoms that may respond to or develop as a result of other medical, surgical, and endoscopic treatments should also be monitored in clinical trials.

**(2.12) In clinical practice, regurgitation should be evaluated routinely** (nature of evidence: E).

**Strength of recommendation:** agree strongly, 31%; agree, reservation, 69%; disagree, reservation, 0%; disagree strongly, 0%.

**(2.13) In clinical trials, regurgitation should be evaluated routinely** (nature of evidence: C).

**Strength of recommendation:** agree strongly, 30%; agree, reservation, 44%; disagree, reservation, 19%; disagree strongly, 7%.

Despite an absence of data, routine evaluation of regurgitation was recommended in both clinical practice and clinical trials as it does not necessarily occur in all patients with heartburn, and vice versa.<sup>86</sup> Further analyses of data from Belgium,<sup>87</sup> undertaken specifically for the workshop, show that in patients with no or mild heartburn, moderate or severe regurgitation is present in some 5% of patients in primary care and 16% in the specialist setting. Regurgitation is an important symptom of reflux disease that should be measured.

**Editorial comment.** Assessment of regurgitation may also be hampered by the lack of standardised description, akin to the "word picture" of "retrosternal burning rising towards the throat" that was developed to standardise the description of heartburn.<sup>22</sup> As indicated above, different therapies may have different effects on these symptoms but the spread of voting in proposition 2.13 reflects recognition that the focus of the trial may not require monitoring of regurgitation.

**What are the outcome variables for long term therapy?**

**(2.14) In clinical trials, a validated measure of patient satisfaction with heartburn control is an important outcome measure for evaluation of long term treatment** (nature of evidence: D).

**Strength of recommendation:** agree strongly, 15%; agree, reservation, 38%; disagree, reservation, 42%; disagree strongly, 4%.

Subjective measures of symptom response are essential, and if a validated measure of patient satisfaction with heartburn control were available, it could be a valuable outcome measure. However, the proposition is difficult to support as no validated instrument exists. A systematic review of comparative studies of surgical and medical therapy

for GORD highlights the numerous outcome measures that have been assessed, including patient satisfaction, but no unifying outcome was expressed, and the results were too heterogeneous for meta-analysis.<sup>88</sup> A study of post-surgical symptoms following open and laparoscopic antireflux surgery showed discrepancies between whether patients would recommend the surgery (similar for both procedures), and their reported satisfaction (lower for laparoscopy) and failure rates (higher for laparoscopy).<sup>89</sup> "Willingness to continue"<sup>89, 90, 91</sup> is probably not a valid or reliable measure of patient satisfaction, and global measures of efficacy do not reflect satisfaction accurately. Patients' expectations influence their satisfaction with treatment and, as expectations may change with ongoing therapy, the assessment of satisfaction, on its own, is a poor measure of efficacy. In conclusion, a validated global measure of patient satisfaction and dissatisfaction is needed to compare outcomes of different therapeutic interventions.

**Editorial comment.** A validated measure of satisfaction could provide a scale by which different treatment modalities could be compared, including surgery, endoscopic therapy, and different medical treatment strategies. This would be of value even though patient satisfaction is dependent, not only on symptom control, but also, among other things, on the knowledge and expectations of patients as well as treatment complications and costs. This opinion was confirmed by broad acceptance of a subsequent proposition to this effect (see proposition 4.12).

**(2.15) Unwillingness to continue treatment due to inadequate control of heartburn should be the primary outcome for clinical trials of on-demand therapy** (nature of evidence: C).

**Strength of recommendation:** agree strongly, 15%; agree, reservation, 30%; disagree, reservation, 52%; disagree strongly, 4%.

Disagreement with this proposition was based on the fact that willingness to continue is influenced by factors other than efficacy, a timescale is not specified, and that evidence is limited for this outcome measure. However, data from six month placebo controlled studies of on-demand therapy in patients with endoscopy negative GORD support the view that discontinuation in these studies is due to inadequate control of heartburn.<sup>89, 90, 91</sup> The primary end point was willingness to continue but separate evaluation of heartburn status shows that discontinuation was virtually entirely due to insufficient control of heartburn. Although not relevant to this proposition, which is specific to clinical trials of on-demand therapy, willingness to continue might be applicable to studies of regular maintenance therapy but it cannot be applied to surgical studies unless the concept could be tested and validated as "unwillingness to continue" after surgery without the use of supplementary therapy (medical, surgical, or endoscopic). A measure is needed that focuses more adequately on the control of reflux symptoms and is thus more broadly applicable, such as "satisfaction with control of heartburn", but see proposition 2.14 above. Further studies are required, preferably over time periods longer than six months, to define more precisely what are the reasons for and implications of a patient's "willingness to continue" therapy. That said, unwillingness to continue is currently a useful outcome measure for clinical trials of on-demand therapy.

**Editorial comment.** One of the difficulties with the concept of "willingness to continue" is that it is not known how it relates to symptom characteristics before, during, and after therapy. However, although there were concerns with "willingness to continue" as an end point, there are difficulties with alternative end points. Pragmatically, although it may not be the optimal outcome measure, willingness to continue is the main measure used currently for studies of

"on-demand" therapy, and it is also relevant to patient management in clinical practice.

Disagreement with the proposition was, in part, because willingness to continue was seen to be influenced by factors other than sufficient control of heartburn. When this concept was reviewed, and inadequate control of heartburn was not specified as the reason for discontinuation, acceptance of the proposition increased (see proposition 2.16).

*(2.16) In long term on-demand trials, unwillingness to continue should be the primary outcome.*

*Strength of recommendation: agree strongly, 4%; agree, reservation, 54%; disagree, reservation, 29%; disagree strongly, 13%.*

Despite the removal of heartburn as a qualifier to describe the reason for discontinuation, over 40% of participants still disagreed with the proposition. This may have been due to use of the phrase "unwillingness to continue" rather than, for example, "happy to continue". However, there was also concern that patients may discontinue therapy because they feel better and not because therapy has failed. "Unwillingness to continue" is a difficult concept which needs further study to define what patients understand by willingness and unwillingness to continue a treatment strategy, as well as the specific treatment related and treatment unrelated reasons why they might discontinue therapy. Outside of the context of clinical studies, it is also important to note that costs and "willingness to pay" on the part of the patient or a third party payer may be determinants of the patient's willingness to continue.

*(2.17) Assessment of treatment efficacy in long term therapeutic trials should include a record of the number of symptom free days (nature of evidence: D).*

*Strength of recommendation: agree strongly, 12%; agree, reservation, 60%; disagree, reservation, 28%; disagree strongly, 0%.*

Heartburn free days is a sensitive measure of efficacy, albeit labour intensive, and although it is unlikely to be the primary outcome measure of a trial, it may provide a more patient centred measure than a change in symptom score. This has been demonstrated for the CADET-HR study<sup>49</sup> in which mean percentage of days spent heartburn free over six months was a greater differentiator of efficacy between omeprazole and ranitidine than willingness to continue, although the study was not designed to compare the two outcomes. "Symptom free days" is sensitive to the cumulative effects of treatment and a more sensitive measure of change than survival curves or symptoms at end point. Numerous practical questions remain however concerning the measurement of symptom free days. Should this be assessed by diary cards, retrospective assessment, telephone contact, or some other technology, such as an electronic diary? Should measurements be conducted daily throughout the trial, recognising that this is labour intensive, or should they be taken for a period prior to the end of the trial or rather at various time points during the trial, recognising that there are no guidelines as to when these assessments should be carried out? There was agreement that further research is needed to answer these questions.

*Editorial comment.* Reservations were based in part on the fact that it may be impracticable, although not impossible,<sup>49</sup> to use daily diary cards in long term studies, and that it is difficult to relate this back to clinical practice. However, if "willingness to continue" is similar between two treatments but there is a large difference in symptom free days, it suggests that "willingness to continue" is an insensitive index of treatment response or that it may be measuring something other than symptom control. Under these circumstances, there is an incentive for the development of a methodology to monitor symptoms on a regular basis,

partly to monitor symptom response to therapy and partly to identify appropriate patients for study.

*(2.18) When on-demand long term drug therapy is being studied in clinical trials, the consumption of medication during the trial should be recorded (nature of evidence: B).*

*Strength of recommendation: agree strongly, 91%; agree, reservation, 9%; disagree, reservation, 0%; disagree strongly, 0%.*

Although not a primary measure of efficacy, consumption of trial medication should be recorded both for information on efficacy and for health economic evaluation. Use of rescue medication (for example, antacid consumption) should also be recorded as a measure of efficacy. Support for this comes from a considerable number of clinical trials of on-demand therapy.<sup>49-50, 51</sup> The dose of trial medication taken, as well as frequency and timing of dose, may provide useful information, including pathophysiological insights into patterns of relapse.

*Editorial comment.* It was recognised that medication intake monitoring is impracticable in clinical practice but that it is useful in clinical research, despite the difficulties inherent in acquiring the data. The development of new technologies, such as "MEMS" (Medical Event Monitoring System) containers,<sup>51</sup> will facilitate monitoring of medication usage, and this should also provide important data for health economic studies.

*(2.19) The same outcome measures of symptom status should be used for trials of drug therapy, antireflux surgery, and other therapeutic interventions (nature of evidence: D).*

*Strength of recommendation: agree strongly, 56%; agree, reservation, 33%; disagree, reservation, 11%; disagree strongly, 0%.*

The overriding argument is that there are increasing numbers of therapies, all for the same disease and, with a broader spectrum of GORD patients now being treated with surgery, it is very important that the same outcome measures be used to assess these different interventions. There is now experience of using the psychological general well being index (PGWBI) and the GSRS to assess the outcomes of surgery. Pretreatment symptoms need to be addressed more effectively in surgery trials, in particular to distinguish these background side effects from true surgery related side effects.

*Editorial comment.* Reservations regarding the proposition were, firstly, that some additional outcome measures would be needed for surgical trials but not necessarily for medical therapy trials and, secondly, that the predictive values of these measures might vary between primary and tertiary care centres. As blinding is virtually impossible in trials of surgical therapy, it is particularly important that measures of symptom status be validated in both medical and surgical treatment populations. All different therapies should be assessed in the same manner to provide comparable data.

*(2.20) The proportions of patients taking drug therapies and the volume of their use following antireflux surgery or other therapeutic interventions are too imprecise for use as a primary efficacy measure in clinical trials (nature of evidence: D).*

*Strength of recommendation: agree strongly, 71%; agree, reservation, 25%; disagree, reservation, 4%; disagree strongly, 0%.*

High rates of antisecretory drug use have been reported following antireflux surgery<sup>52</sup> but this may be inappropriate use.<sup>53</sup>

*Editorial comment.* Although the proposition was accepted as written, medication use remains an important secondary outcome measure as it reflects an intention to treat outcome and it is important for health economic studies, particularly when comparing medical and surgical therapies.

Furthermore, there are few data on the proportions of patients in long term medical studies who may take their medication for reasons other than heartburn control.

**(2.21) Absence of heartburn after an initial course of therapy is a good predictor of freedom from oesophagitis** (nature of evidence: A).

*Strength of recommendation:* agree strongly, 85%; agree, reservation, 15%; disagree, reservation, 0%; disagree strongly, 0%.

Recent comparative studies in patients with reflux oesophagitis have shown that absence of heartburn with esomeprazole corresponds with absence of oesophagitis in at least 80% of patients.<sup>17-26</sup> Based on the analysis by Sharma and colleagues<sup>1</sup> in this supplement (see page iv58-iv65), correlation of absence of heartburn with healing of oesophagitis is excellent. Overestimation of healing by the absence of heartburn is approximately 5% but this overestimate rises to 28% when reduction in heartburn is used as a predictor of oesophagitis healing. Absence of heartburn thus seems to be a suitable surrogate marker for healing of oesophagitis during short term (4-8 week) therapy although this needs further investigation, particularly documenting clinician versus patient self-assessment of the absence of heartburn.

*Editorial comment.* A qualifier to the conclusion from the analysis by Sharma and colleagues<sup>1</sup> in this supplement (see page iv58-iv65) is that absence of heartburn and healing of oesophagitis do not necessarily occur concurrently in the same patients.<sup>24</sup> Additionally, the nature of the evidence may be an overestimate because although the data are derived from randomised controlled trials, studies were not designed to assess the relationship between symptoms and healing in a randomised fashion.

**(2.22) Absence of heartburn during continuous long term therapy is a good predictor of freedom from oesophagitis** (nature of evidence: A).

*Strength of recommendation:* agree strongly, 87%; agree, reservation, 13%; disagree, reservation, 0%; disagree strongly, 0%.

The systematic review by Sharma and colleagues<sup>1</sup> in this supplement (see page iv58-iv65), based on seven trials of antisecretory maintenance therapy, shows that absence of heartburn and absence of oesophagitis are well correlated. Absence of moderate to severe symptoms overestimated oesophagitis remission by approximately 9%. Similarly, in a meta-analysis of five randomised long term trials with omeprazole, asymptomatic relapse of oesophagitis was only found in 8.6% of patients.<sup>24</sup>

*Editorial comment.* Again, as for proposition 2.21, the nature of the evidence may be an overestimate as studies were not designed to assess the relationship between recurrent symptoms and recurrent oesophagitis in a randomised fashion, even though these data were derived from randomised controlled trials.

**Are there symptom patterns that predict outcome for therapy of reflux disease?**

**(2.23) Absence of heartburn after one week of PPI therapy predicts sustained symptom reduction after four weeks of therapy** (nature of evidence: B).

*Strength of recommendation:* agree strongly, 12%; agree, reservation, 88%; disagree, reservation, 0%; disagree strongly, 0%.

Pooled data from studies of esomeprazole in endoscopy negative reflux disease have shown that heartburn response during days 5-7 of the first week of therapy is the most discriminating predictor of treatment outcome although it was a secondary objective of the trials from which the data were derived.<sup>29</sup> Of patients who were heartburn free for days 5-7 of treatment, 85% were heartburn free at week 4 while of patients with moderate or severe heartburn every day for

days 5-7, only 22% were heartburn free at week 4. Comparable data however are not available for patients with reflux oesophagitis. Also, the symptom response at four weeks may not be the gold standard because a proportion of patients who are symptomatic at four weeks may still become symptom free with more prolonged therapy. Knowledge that a patient responding at one week will continue to respond at four weeks is of value in clinical practice although the converse does not apply; a lack of response at one week does not necessarily mean that the patient will not respond at four weeks.

*Editorial comment.* Although early abolition of heartburn symptoms is predictive of a more sustained response, assessment of symptoms after one week of treatment probably has low specificity for the diagnosis of reflux related symptoms. This presumption should be tested prospectively, particularly because of widespread interest in the clinical potential of a "PPI test" or acid suppression test for the diagnosis of GORD and acid related disorders.<sup>13-26</sup>

**(2.24) Nocturnal heartburn at baseline is an important predictor of failure of PPI therapy** (nature of evidence: C).

*Strength of recommendation:* agree strongly, 0%; agree, reservation, 12%; disagree, reservation, 52%; disagree strongly, 36%.

Indirect evidence indicates that nocturnal heartburn, although common, is not a predictor of relapse or PPI treatment failure. Studies with both ranitidine<sup>30</sup> and esomeprazole<sup>31</sup> have shown that improvement in daytime heartburn with PPI therapy is paralleled by improvement in nocturnal heartburn although this was a secondary study objective. An analysis of pooled studies with esomeprazole in a total of approximately 12 000 reflux oesophagitis patients shows that 42% had night-time symptoms at baseline. After four weeks of treatment, only 15% still had nocturnal heartburn. Although these data were part of a secondary analysis, they suggest that nocturnal heartburn improves in as many patients as does daytime heartburn. However, it may be that persistent nocturnal heartburn after initial therapy is more difficult to treat (or more troublesome to the patient) than persistent daytime heartburn, but this does not necessarily mean that nocturnal heartburn is a predictor of treatment failure.

**(2.25) Patients with multiple symptom patterns at baseline have a lesser response to PPI therapy** (nature of evidence: D).

*Strength of recommendation:* agree strongly, 23%; agree, reservation, 73%; disagree, reservation, 4%; disagree strongly, 0%.

Evidence in support of this proposition is limited. There are unpublished post hoc analyses of studies in endoscopy negative GORD patients which show that reflux symptoms respond less well to PPI therapy in patients who have more non-heartburn symptoms, as assessed by the GSRS (AstraZeneca, data on file). The percentage of patients with absence of heartburn at four weeks is lower in patients with over 13 GSRS items, including, for example, diarrhoea, than in those with only one or two items. A minority of GORD patients have multiple unexplained symptoms which may be associated with other psychological distress and, in general, medical and surgical treatments have been shown to be less effective in somatising patients.<sup>100</sup> In addition, patients with uninvestigated heartburn dominant dyspepsia are less likely to respond to initial therapy if they have concomitant symptoms of irritable bowel syndrome.<sup>64-101</sup>

*Editorial comment.* This proposition raises a matter that is particularly important for the treatment of endoscopy negative reflux disease patients or patients with uninvestigated reflux symptoms. Proposition 2.11 addressed the need to monitor symptoms other than heartburn and, in clinical trials, it may also be necessary to consider a prospective study



of the role of other symptoms as predictors of treatment response. Again, as with proposition 2.24, there is no indication that the impact of multiple symptoms on outcome is specific to PPI therapy, or that they are predictive, specifically, of PPI treatment failure

How should extra-oesophageal symptoms, ascribed to reflux, be monitored during therapy?

(2.26) *The response to treatment of extra-oesophageal symptoms caused by reflux occurs typically over weeks, rather than days* (nature of evidence: E).

*Strength of recommendation: agree strongly, 0%; agree, reservation, 60%; disagree, reservation, 32%; disagree strongly, 8%.*

The spread of voting reflects the lack of evidence, and support for the proposition was based largely on empirical clinical experience that prolonged therapy is of value. A single study has shown that asthma symptom scores continue to decline over three months during omeprazole therapy<sup>102</sup> but the data are based on low patient numbers and are confounded by the fact that responders had more severe baseline symptoms than non-responders. Thus the symptoms of "responders" could just have been regressing to the mean with time, rather than therapy. Studies of treatment of suspected reflux laryngitis,<sup>103</sup> GORD related asthma,<sup>104</sup> and GORD and cough<sup>105</sup> have typically involved treatment of at least four weeks, and frequently longer, but the results are quite heterogeneous and confounded by the use of different, frequently high dose, therapies.

*Editorial comment.* Ear, nose, and throat (ENT) symptoms in laryngitis patients, measured by the reflux symptom index (RSI) symptom scale, have been shown to respond to PPI therapy within two months while those assessed by the reflux finding score (RFS) took 4–6 months to respond, although these measures are not validated.<sup>106</sup> Thus the above data should be qualified by the comment that a four month difference in the time to response may reflect the measurement instrument rather than the disease. It should also be noted that even typical reflux symptoms do not necessarily respond rapidly, and that there is an increase in the proportion of erosive oesophagitis patients who achieve symptom reduction as treatment is continued up to four weeks,<sup>16, 73, 74</sup> and beyond, to eight weeks.<sup>107</sup> Thus it is quite reasonable to suppose that reflux related respiratory tract symptoms may take many weeks to resolve.

(2.27) *The measurement tools needed to assess the treatment response of extra-oesophageal symptoms are different from those needed to assess the response of heartburn to treatment* (nature of evidence: E).

*Strength of recommendation: agree strongly, 83%; agree, reservation, 17%; disagree, reservation, 0%; disagree strongly, 0%.*

There is little documentation for this proposition but extra-oesophageal GORD is quite different from traditional GORD. Heartburn, regurgitation, and oesophagitis are often absent in patients with extra-oesophageal GORD who may have multiple aetiologies for their extra-oesophageal symptoms and signs. Consequently, the measurement tools for these symptoms clearly need to be different from those used in traditional GORD patients. Potential objective parameters include peak expiratory flow rates, spirometry, ENT examination, and cough meters. However, spirometry has not been shown to be useful, and interobserver variability is very poor for ENT examinations of the mucosa.<sup>108</sup> Potential subjective parameters include questionnaires for asthma, cough,<sup>109</sup> and ENT complaints (such as the RSI and RFS),<sup>106</sup> but these require validation. This is an area requiring considerable further research, including the development of new validated measurement tools and a better understanding of the

pathogenesis of oral, ENT, and respiratory conditions that are ascribed to gastro-oesophageal reflux.

*Editorial comment.* Tools designed to measure the severity of symptoms, such as heartburn, are very unlikely to be valid in the assessment of dyspnoea, cough, wheezing, or dysphonia.

### Future directions

Consideration of the practicalities of reflux symptom severity assessment summarised above defined many areas that need further study.

One overriding dilemma relates to the definition of relevant reflux symptoms. Future research is needed into this. Many patients experience other symptoms, in addition to heartburn, and these symptoms may respond differently to therapy. To date, the majority of studies have concentrated on heartburn as the primary outcome variable. This is the most prevalent symptom and the one that responds most predictably to acid suppression therapy but other symptoms should also be assessed in conjunction with heartburn. One approach, to use a global outcome score, has the advantage that it would encompass the overall response to therapy. However, the disadvantage is that inclusion of symptoms that are less likely to respond to therapy may render the score less sensitive as a measure of treatment outcome. The use of a global score is complicated further by the fact that heartburn is a common, and possibly incidental, symptom in patients who may have many other symptoms of functional bowel disorders, including dyspepsia and irritable bowel syndrome. Prediction of a poorer response to PPI therapy by the presence of multiple symptoms (see proposition 2.25) indicates the need to determine whether patients with dominant heartburn respond differently from those with non-dominant heartburn. Similarly, regurgitation may not respond as well to therapy as heartburn, and it will be important to conduct prospective studies of therapy in patients who have regurgitation as their dominant or only symptom.

There is a continuing need to improve the translation of clinical trial outcomes into clinical practice. Abolition of symptoms may be an important outcome in clinical research but it is an unrealistic expectation for many patients in day to day practice. In consequence, it will be important to define better the relationship between abolition of symptoms and clinically acceptable outcomes, including measures of patient satisfaction.

As reflux symptoms vary considerably in severity and frequency between and within individuals, better techniques are needed (for example, using a personal digital assistant, mobile phone, or two way pager) for recording symptoms on a daily basis without the difficulties attributable to recall bias, compliance, or hoarding that hamper the use of a daily diary card. Modified Likert seven point scales should also be validated across the spectrum of reflux related symptoms, including patients with heartburn dominant, heartburn non-dominant, and extra-oesophageal symptoms. Additionally, changes in symptom severity should be correlated with clinically relevant outcomes to define minimal clinically important treatment related changes for these other symptoms. Related to this, "word pictures", akin to that developed to describe heartburn, are likely to help patients understand and report less typical symptoms of reflux disease more objectively and reliably.

Assessment of outcomes in long term therapy of reflux disease is particularly difficult, partly because expectations appear to change during its therapy, and partly because of the range of different treatment options and strategies. "On-demand" medical therapy is a useful option for the management of milder or less frequent symptoms. There is a need for further research into the temporal pattern of symptom occurrences during such therapy and the factors that drive

"on-demand" use of medication. More needs to be known about the natural history of symptom recurrence in GORD, and the factors that determine a patient's willingness to continue an established management strategy, whether it be "on-demand" medical therapy or use/rejection of rescue therapy to treat recurrent symptoms after a surgical or endoscopic antireflux procedure. It seems reasonable to assess symptom free days and medication usage (including active therapy and rescue therapy) during long term therapy to determine treatment efficacy and the health economic implications of different management strategies. The practicalities of making these measurements reliably are challenging, as these measures are subject, like daily diaries, to confounding by recall bias, compliance, and hoarding. Again, new technologies may avoid some of the difficulties experienced to date in acquiring these data.

The pathophysiological mechanisms responsible for the generation of reflux symptoms, whether they be typical oesophageal symptoms or atypical extra-oesophageal symptoms, are poorly understood. A better understanding of these mechanisms may help determine which patients will respond to therapy and will facilitate prospective studies to identify predictors of symptom response across the spectrum of reflux related diseases.

In conclusion, assessment of symptom severity is fundamental to the management of reflux disease but there is much still to be done to optimise the treatment of patients with this very common condition.

### 3. QUALITY OF LIFE: PROPOSITIONS, VOTING, DISCUSSION, AND COMMENTARY

#### Introduction

Quality of life is a dynamic construct and therefore inherently difficult to assess as time of assessment will affect the responses given. Moreover, quality of life may not be adequately represented in the impact of the disease on a patient's daily activities, such as sleep and work, as assessed by quality of life questionnaires, but can be defined more broadly as the gap between a patient's expectation and experience. Furthermore, quality of life measures need to be patient centred rather than reflecting what clinicians think is important.

Although there has been considerable discussion of the importance of patient quality of life as an outcome of therapy, surprisingly, it has rarely been assessed in clinical trials. The systematic review by Sharma and colleagues<sup>1</sup> in this supplement (page iv58-iv65) found that of 157 publications on long term medical therapy for GORD, 48 were eligible and from these, data were extractable from only 37. Of these, only three assessed patient quality of life, two using the PGWBI and one using SF-36. For short term therapy, 126 publications were eligible, and data were extractable from 108, of which six measured quality of life. One publication used the PGWBI, one used SF-36, two used other generic measures, and two used disease specific measures. Thus of 174 eligible randomised controlled trials in GORD, only nine assessed patient quality of life as an outcome.

If patient quality of life is to be a key outcome in clinical trials in GORD, guidance is needed on how best to measure and interpret changes in quality of life. Should measurement be based on utilities or domains, and should measures be generic or disease specific? If disease specific measures are used, are they really just symptom impact scores? In clinical practice, adaptation is often observed whereby patients adjust to the quality of life they have, so how practical is measurement of patient quality of life in clinical practice, particularly as it could be time consuming? Can quality of life measures be a substitute for symptom measures and will they serve to raise patient expectations?

These questions, relating to quality of life and symptom assessment in GORD, were addressed in the workshop under five topic areas.

- Should generic or disease specific measures of quality of life be used in determining response to therapy in clinical trials?
- How frequently should quality of life be measured in trials in reflux disease?
- How should changes in quality of life be reported in trials?
- Is "symptoms sufficient to impair quality of life" a meaningful concept for defining presence of reflux disease in clinical trials or practice?
- Do quality of life measures correlate with other outcome measures?

Should generic or disease specific measures of quality of life be used in determining response to therapy in clinical trials?

(3.1) *Disease specific measures of quality of life are more responsive to changes in the impact of reflux symptoms in response to therapy* (nature of evidence: C).

Strength of recommendation: agree strongly, 25%; agree, reservation, 71%; disagree, reservation, 4%; disagree strongly, 0%.

Generic measures, such as the SF-36, are less responsive to symptom improvement in GORD than disease specific questionnaires.<sup>10</sup> In the ProGERD study of esomeprazole therapy, the effect sizes (standardised means) in components of the SF-36 were approximately 0.3–0.5 compared with over 1.0 with the disease specific QOLRAD instrument,<sup>11</sup> while the physical and mental components of the SF-36 were unable to detect changes in GORD patients treated with lansoprazole or ranitidine.<sup>12</sup> A disease specific measure of quality of life should therefore be used to assess the impact of GORD symptoms in response to therapy. Addition of generic measures would serve to increase clinical trial burden considerably.

(3.2) *Generic measures of quality of life are appropriate for making comparisons of disease impacts across different diseases* (nature of evidence: B).

Strength of recommendation: agree strongly, 100%; agree, reservation, 0%; disagree, reservation, 0%; disagree strongly, 0%.

The relative benefits and shortcomings of generic versus disease specific quality of life measures are well recognised,<sup>13</sup> and while generic measures are appropriate for making comparisons across diseases, disease specific measures are, by definition, inappropriate for this purpose. There are numerous examples of the use of generic measures, such as the SF-36 questionnaire, to compare the impact of diseases on quality of life—for example, comparing GORD with heart failure and clinical depression.<sup>14–15</sup>

*Editorial comment.* There is clearly a trade off implied by the last two propositions. On the one hand, efficient trial design demands a responsive and, therefore, disease specific measure. On the other hand, if any comparison with other disease states is likely, a generic population validated measure, such as the EuroQol, should be used. These are particularly appropriate when health economic outcomes are being considered.

(3.3) *In clinical trials of reflux disease, measurement instruments must be validated for both the language and culture of participating patients* (nature of evidence: B).

Strength of recommendation: agree strongly, 37%; agree, reservation, 59%; disagree, reservation, 4%; disagree strongly, 0%.

Some work has been done on multiple translations of the SF-36 questionnaire<sup>16</sup> and the development of cross cultural

questionnaires."<sup>17</sup> Anecdotal evidence suggests that the QOLRAD instrument performs similarly in different countries. However, validation of measurement instruments for different cultures is needed. Although expensive, formal translation may not be enough, given that wording is interpreted differently between countries, and language, responsiveness, and reliability all need validating. This may not be practical in every language and culture. Further research should determine a core set of items that could be used in cross cultural studies in the area of GORD.

**How frequently should quality of life be measured in trials in reflux disease?**

**(3.4) Measurement of quality of life at baseline and at the end of initial therapy or at dropout is sufficient for clinical trials of initial drug therapy** (nature of evidence: C).

Strength of recommendation: agree strongly, 19%; agree, reservation, 58%; disagree, reservation, 23%; disagree strongly, 0%.

The proposition would not be valid if patient quality of life showed significant variations during the course of therapy, rather than a progressive improvement. There are no data on daily quality of life in GORD patients treated with anti-secretory therapy but the few studies which have made more than one quality of life assessment after baseline support the view that there is a progressive improvement in patient quality of life during therapy.<sup>118-120</sup> In the study by Talley *et al* in patients with endoscopy negative GORD treated with esomeprazole or omeprazole, GSRS symptom scores improved in parallel with QOLRAD scores, with no clinically significant differences at two and four weeks. In reflux oesophagitis patients treated with esomeprazole,<sup>120</sup> heartburn severity and QOLRAD scores improved dramatically at four weeks, with a small additional improvement at eight weeks. Measurement of quality of life at baseline and at the end of initial therapy or at dropout is probably therefore sufficient for clinical trials of initial drug therapy although measurement at dropout is an important qualification.

**Editorial comment.** The dissenting opinion on this proposition relates partly to the wording of "sufficient", and the lack of evidence from multiple time points rather than two time points. Dissenting opinion also relates to the use of disease specific or generic measures of quality of life and the nature of the intervention. While the evidence presented supports the proposition that quality of life improves with treatment, the evidence is limited to disease specific measures and continuous therapy. Generic measures may be subject to competing influences on quality of life during the course of the trial and adaptation may also occur, reducing the impact of health status change. In addition, intermittent therapies, such as on-demand therapy, may result in fluctuating quality of life. This concept is addressed by the following proposition.

**(3.5) For clinical trials of continuous long term therapy of any type, time based measurement (for example, at yearly intervals) of quality of life is the most appropriate indicator** (nature of evidence: E).

Strength of recommendation: agree strongly, 18%; agree, reservation, 64%; disagree, reservation, 14%; disagree strongly, 4%.

**(3.6) For clinical trials of intermittent long term therapy, event based measurement of quality of life is most appropriate** (nature of evidence: B).

Strength of recommendation: agree strongly, 0%; agree, reservation, 22%; disagree, reservation, 70%; disagree strongly, 7%.

There is very little evidence with which to address these propositions, and recommendations must be based on expert opinion. Time based evaluations are administratively convenient and appropriate where quality of life is expected to be relatively stable over time although they may not capture the

variation in relapsing-remitting conditions or on-demand therapies, particularly with less frequent assessments or smaller sample sizes. Time based evaluations are appropriate for comparison of two or more continuous long term therapies, with the reservation that the choice of assessment interval will depend on the nature of therapy, including surgery, and yearly intervals may not be adequate.

Event based evaluations are less convenient to administer as knowledge is needed of when the event occurs, be it a clinical event or change in therapy. If appropriately timed, event based measurements are likely to be more responsive when quality of life is expected to fluctuate over time and, in theory, they are appropriate for comparison of intermittent therapies. However, the proposition was rejected because of problems with its practicability, and the potential for bias if event related measurement in one trial group led to a significant difference in the timing of measurements between groups. A further issue is what form of measurement to use for comparison of continuous and intermittent therapy. In this case, regular, and more frequent, time based evaluations, with a large sample size, may be more appropriate than event based measurement.

**Editorial comment.** The group quite consistently rejected the notion of event based measurement, preferring the alternative option of more frequent measurement intervals, and accepting that some events might be missed.

**How should changes in quality of life be reported in trials?**

**(3.7) Reporting of subscales in quality of life measures is the most responsive measure of change in trials provided that adjustment is made for multiple testing and end points are prespecified** (nature of evidence: C).

Strength of recommendation: agree strongly, 24%; agree, reservation, 68%; disagree, reservation, 8%; disagree strongly, 0%.

Data from a single study of endoscopy negative reflux disease patients treated with esomeprazole or omeprazole indicate that subscales are more responsive than global scores.<sup>42</sup> Subscales of the QOLRAD were highly responsive, and effect sizes were impressive.

**Editorial comment.** This is to be expected, as GORD principally affects dimensions relating to pain, emotion, and physical function, having less effect on other dimensions. The effects on global scores are therefore somewhat diluted. This may be less so with disease specific measures, which focus more on aspects of quality of life relevant to particular diseases.

**(3.8) Reporting population derived QALYs (quality adjusted life years) is most appropriate for cost utility studies from the third party payer's perspective** (nature of evidence: D).

Strength of recommendation: agree strongly, 4%; agree, reservation, 35%; disagree, reservation, 54%; disagree strongly, 8%.

**(3.9) Reporting patient derived QALYs is most appropriate for cost utility studies from the patient's perspective** (nature of evidence: D).

Strength of recommendation: agree strongly, 0%; agree, reservation, 35%; disagree, reservation, 54%; disagree strongly, 12%.

These were largely rejected because of the lack of adequate utility measures in GORD. Without these, the propositions cannot be recommended as "the most appropriate". However, the workshop recognised that there will be increasing pressure from health care and research funding bodies to incorporate utility measures in GORD studies, and various public health bodies are promoting QALYs for the measurement of health care. This cannot be ignored, and the lack of patient centred end points in studies is a drawback.

Further work is needed to define the appropriate means of eliciting utility measures in GORD.

*Editorial comment.* QALYs are years of life multiplied by the utility of each year of life on a scale of 0 to 1, where 1 is perfect health and 0 is death. Thus 10 years of life at a utility of 0.5 would be 5 QALYs.<sup>121</sup> The whole concept of "population derived" QALYs can be criticised in that the methods used to assess them are based on presenting scenarios to healthy individuals and ascertaining their expectation of the health state described, rather than their experience of the actual health state. Critique from the perspectives of cognitive psychology and sociology<sup>122</sup> suggests that this is likely to be unreliable. The principal criticism is that subjects not directly experiencing the disease state fail to take adaptation into account.

Is "symptoms sufficient to impair quality of life" a meaningful concept for defining presence of reflux disease in clinical trials or practice?

(3.10) *For clinical trials, symptoms are a more appropriate entry and outcome measure than quality of life measures* (nature of evidence: C).

*Strength of recommendation:* agree strongly, 65%; agree, reservation, 23%; disagree, reservation, 8%; disagree strongly, 4%.

Although changes in some dimensions of quality of life measures, such as food and drink problems, are very important to patients, the magnitude of change of quality of life measures is not as great as change in heartburn symptoms.<sup>123</sup> Thus while quality of life measures provide useful information, heartburn, and possibly regurgitation, are the most important entry and outcome measures for clinical trials in GORD.

*Editorial comment.* Although symptoms were seen to be a more appropriate entry and outcome measure than quality of life measures in clinical trials, quality of life measures are of potential value if used to assess secondary outcomes. They may also provide information on any adverse impact of intervention. This was recognised in a further proposition (3.11) that was fully accepted.

(3.11) *A quality of life measure that is responsive and measures multiple dimensions validly should be used to assess secondary outcomes in clinical trials.*

*Strength of recommendation:* agree strongly, 69%; agree, reservation, 31%; disagree, reservation, 0%; disagree strongly, 0%.

(3.12) *For clinical practice, exploration of the impact of symptoms on patient quality of life is an important part of the assessment of adequate therapy* (nature of evidence: E).

*Strength of recommendation:* agree strongly, 38%; agree, reservation, 38%; disagree, reservation, 23%; disagree strongly, 0%.

There is no evidence in the area of GORD to support this proposition but it has a strong theoretical basis in the ideas of holistic care, patient centeredness, and shared decision making. The only indirect evidence comes from a systematic review of the effect of formal decision aids on patient outcomes which found that they increased patient knowledge and reduced decisional conflict but did not increase satisfaction.<sup>124</sup> The main reservation with the proposition was that quality of life parallels symptom assessment. However, quality of life may not be concordant with symptom control. Patients with good symptom control may have impaired quality of life (for example, due to dietary restrictions) while, conversely, patients may have a good quality of life despite residual symptoms because they have adjusted their expectations. The marginal cost effectiveness of moving from minimal but tolerated symptoms to complete abolition will be very low, emphasising the value of exploration of the

impact of symptoms on patient quality of life, which should be routine clinical practice.

(3.13) *A self-administered quality of life questionnaire can be used in conjunction with a symptom score to assess the presence or absence of reflux disease* (nature of evidence: E).

*Strength of recommendation:* agree strongly, 0%; agree, reservation, 4%; disagree, reservation, 85%; disagree strongly, 11%.

No data exist to support this proposition. Quality of life is impaired in proportion to symptom severity<sup>124</sup> while GORD treatment improves symptom severity and quality of life proportionately.<sup>125</sup>

*Editorial comment.* In the absence of data demonstrating value of quality of life measurement on top of symptom assessment in the diagnosis of GORD, the additional burden cannot be justified, and the proposition was therefore rejected. Note that this is distinct from assessing the outcome of therapy where quality of life measurements do have a useful role.

(3.14) *A self-administered symptom scoring system used in conjunction with a quality of life questionnaire is more reliable than a global clinical opinion to assess the presence or absence of reflux disease* (nature of evidence: E).

*Strength of recommendation:* agree strongly, 0%; agree, reservation, 0%; disagree, reservation, 19%; disagree strongly, 81%.

The proposition implies that a self-administered symptom scoring system and quality of life questionnaire is better than clinical assessment, for which there are no data. Rejection of the proposition, though, assumes that the clinical interview is technically adequate in assessing the patient.

*Editorial comment.* Taken together, propositions 3.13 and 3.14 indicate that global clinical opinion, based on a technically adequate clinician interview, is the most accurate approach to the diagnosis of GORD, rather than a self-administered symptom scoring system for the patient, coupled with a quality of life questionnaire. This is a key recommendation and is consistent with proposition 1.11, which specifies the physician interview as the means of diagnosing predominant heartburn.

Do quality of life measures correlate with other outcome measures?

(3.15) *Quality of life measures correlate well with frequency of heartburn* (nature of evidence: C).

*Strength of recommendation:* agree strongly, 25%; agree, reservation, 71%; disagree, reservation, 4%; disagree strongly, 0%.

Unpublished data from the ProGERD study (AstraZeneca, data on file) support the proposition, showing a good correlation between the frequency of heartburn and the dimensions of both the QOLRAD and SF-36 scales.

(3.16) *Quality of life measures correlate well with severity of heartburn* (nature of evidence: A).

*Strength of recommendation:* agree strongly, 48%; agree, reservation, 52%; disagree, reservation, 0%; disagree strongly, 0%.

Quality of life measures have been shown to correlate well with the severity of heartburn for the QOLRAD,<sup>126</sup> PGWBI,<sup>127</sup> and SF-36 scales.<sup>128</sup> The majority of data relate to the response to short term therapy, and data are required on long term changes in quality of life in relation to symptom severity, as well as symptom frequency, overall treatment effect, and patient satisfaction.

*Editorial comment.* Although both these propositions (3.15 and 3.16) were supported, the evidence was limited to one trial and one measure for heartburn frequency, and three trials for severity. Early reports of effects frequently suggest a stronger effect than is subsequently confirmed by later studies. Much more evidence is needed before it can be

implied that symptom response can be taken as a proxy for improvement in quality of life.

(3.17) *Changes in quality of life correlate well with patient satisfaction with treatment* (nature of evidence: C).

Strength of recommendation: agree strongly, 0%; agree, reservation, 18%; disagree, reservation, 71%; disagree strongly, 11%.

Data are available from one study to support a weak correlation between quality of life and patient satisfaction in GORD<sup>62</sup> but quality of life scores have been reported not to predict patient satisfaction in reflux oesophagitis patients treated with on-demand therapy.<sup>126</sup> In other conditions, a lack of correlation has been reported for psychiatric care,<sup>127</sup> diabetes care,<sup>128</sup> and cancer nursing.<sup>129</sup> Patient satisfaction is determined by age, anxiety, self-perceived health status, and expectations. It is also influenced by the process and overall quality of healthcare, and so a patient may have a good quality of life but poor satisfaction if, for example, they have had a long wait for endoscopy. Thus a complete correlation may not be expected between quality of life and patient satisfaction. Patient expectation and satisfaction is addressed in more detail in the next paper.

#### Future directions for research

Many more randomised clinical trials need to include quality of life measures as an outcome. This would provide more data on the following areas.

- Associations between symptom improvement, changes in quality of life, and patient satisfaction. Proposition 3.13 was rejected on the basis that there is insufficient evidence to support incorporation of quality of life measurement into the disease definition of GORD. Support could come from well designed studies examining the relationship of symptom changes (both frequency and severity) with quality of life and patient satisfaction. It needs to be shown whether the addition of quality of life measurement adds anything to symptom measures.
- Relationships between changes in disease specific measures and changes in commonly used generic quality of life measures. This is needed to help resolve the tensions between responsiveness, generalisability, and the burden on research subjects of being given multiple measures.
- Role of quality of life measurement in the diagnosis of reflux disease.
- Change in quality of life over time with different therapies, and without intervention. Propositions 3.5 and 3.6 showed that there was a great need to determine when is the most appropriate time to assess quality of life in long term trials, particularly of intermittent therapy.
- Effects of long term treatment on quality of life.

In addition, the methodology of quality of life measurement itself faces challenges, particularly in the following areas.

- More research in the translation of generic quality of life measures into utility based measures and QALYs, taking into account response shift.
- Simpler measures that might be used to audit the quality of clinical care. Proposition 3.14 was strongly rejected on the basis of an absence of a simple score that might augment a clinical interview.
- More research on cross cultural and cross language validation of quality of life measures. Proposition 3.3 was accepted with reservation owing to the lack of evidence as to the degree of validation required.

## 4. PATIENT EXPECTATIONS AND SATISFACTION: PROPOSITIONS, VOTING, DISCUSSION, AND COMMENTARY

### Introduction

The three main determinants of a patient's satisfaction with treatment are clinical outcome, interpersonal care and relationship with the physician, and the physical environment of the health care process.<sup>130</sup> In parallel with this, patient expectations can vary according to knowledge and prior experience, and can be changed by the physician, and may also change with accumulating experience. Moreover, patients new to a disease and the therapies available may not really know what their expectations are. Expectations are also affected by culture, socioeconomic status, personal values, attitudes, education, and knowledge.

Given this dynamic, multifactorial nature of patient expectation and satisfaction, it is not surprising that presentation of patient satisfaction results alone, without the context of efficacy and safety results, can be misleading. Patients may be happy with the process of care (for example, access to physicians, the physical environment of the facility, etc), even though their state of health is no better following treatment. Conversely, a patient's health may be greatly improved by treatment but their satisfaction is low because they are unhappy with the process of care that they experienced. This is exemplified by data from 80 GORD patients following laparoscopic fundoplication.<sup>131</sup> Most patients responded to a global question regarding satisfaction by indicating they were satisfied despite persistent GORD symptoms or the development of new symptoms, such as dysphagia, which were severe enough to impair quality of life measured by a disease specific instrument.

This underlines the potential lack of correlation between global patient satisfaction data and clinical outcomes. It also highlights the fact that patient satisfaction alone is an imperfect measure of disease management, particularly when patient expectations are low. In a cross sectional survey of chronic heartburn sufferers,<sup>132</sup> 45% of patients treated with H<sub>2</sub> receptor antagonists and 58% of patients receiving PPIs were totally satisfied with treatment. The low rate of satisfaction with PPI therapy is surprising, given their high efficacy rates. The study did not address the causes of satisfaction and dissatisfaction. Did patients experience inadequate symptom control or were they not happy with the process or cost of care, and what were their expectations in the first place? This raises numerous questions about the role of patient expectation and satisfaction in clinical practice and clinical trials in GORD, and the validity of the instruments currently available in this area.

Questions related to patient expectation and satisfaction, and symptom assessment in GORD, were addressed in the workshop under four topic areas.

- Why is measurement of patient satisfaction important in reflux disease?
- How should patient satisfaction be measured?
- Are patients satisfied with current therapy for reflux disease?
- How important are patient expectations in determining patient satisfaction?

### Propositions, voting, and discussion

Why is measurement of patient satisfaction important in reflux disease?

(4.1) *Patient satisfaction is an important outcome measure in the treatment of reflux disease* (nature of evidence: D).

Strength of recommendation: agree strongly, 32%; agree, reservation, 50%; disagree, reservation, 14%; disagree strongly, 4%.



The proposition relates to routine clinical practice, rather than clinical trials, and recommends patient satisfaction as one of several outcome measures, not the sole measure. In this context, although there are no direct data to support it, the proposition is correct, since evaluation by the clinician of patient satisfaction, and definition of their expectations, is a routine clinical skill. It is intuitive to measure satisfaction with therapy, and to determine if reasonable expectations are being met. However, this has not been formalised into a validated tool with which to measure patient satisfaction in GORD. Such a formal measure needs to accurately reflect impacts of therapy, be referenced to appropriate patient expectations, and not be unduly influenced by psychological and functional variables that are not directly linked to reflux disease symptoms. It needs to be a validated standardised scale that can be compared across groups and studies.

*Editorial comment.* It is clearly desirable to have a satisfied patient in clinical practice. This vote reflects the view that while it is a useful outcome measure it cannot be important until proper tools to evaluate it become available. This view is reflected also in the rejection of the propositions related to the use of patient satisfaction as outcome measures in assessing treatment response (propositions 2.2 and 2.14).

**(4.2) Systematic use of patient satisfaction data enables choices to be made between alternatives in the organisation or provision of health care for reflux disease** (nature of evidence: B).

*Strength of recommendation:* agree strongly, 0%; agree, reservation, 12%; disagree, reservation, 77%; disagree strongly, 12%.

Conceptually, the proposition is acceptable, but practically it is not, and it was therefore rejected. Systematic use of patient satisfaction data is not possible in the absence of validated tools with which to measure it.

*Editorial comment.* Patient satisfaction data are widely used by managed care organisations to provide comparisons between plans and physician groups. These may be useful measures of the process of care. There are no validated tools in GORD that can separate the process of care from clinical outcomes. This vote reflects the lack of confidence that patient satisfaction can replace clinical outcome data in making determinations about treatment choices for reflux disease.

**How should patient satisfaction be measured?**

**(4.3) Patient satisfaction surveys require appropriate methodology and validated instruments** (nature of evidence: B).

*Strength of recommendation:* agree strongly, 96%; agree, reservation, 0%; disagree, reservation, 4%; disagree strongly, 0%.

Current measures of patient satisfaction are inappropriate, as they have no conceptual model, few include qualitative patient data, they are mostly simple single item scales, there are problems with response bias, and psychometric data are limited. Consequently, they result in biased measurement and decreased ability to detect small but meaningful differences in outcome. The rationale for supporting the proposition is the potential value of a validated measure of patient satisfaction, which can provide an overall assessment of health care delivery from the patient's standpoint.

*Editorial comment.* The nature of evidence may be an overestimate, as support of this proposition is largely based on expert opinion. Global estimates are useful to identify deficiencies in the process of care (scheduling of appointments, wait times, responsiveness of staff, etc).

**(4.4) There are several important dimensions of patient satisfaction relevant to reflux disease treatment** (nature of evidence: E).

*Strength of recommendation:* agree strongly, 30%; agree, reservation, 63%; disagree, reservation, 7%; disagree strongly, 0%.

Treatment satisfaction in GORD decreases with increasing disease severity but there is a large disconnect between patient satisfaction and treatment outcome in that satisfaction is not related to the extent of symptom reduction (see Revicki<sup>133</sup> in this supplement (page iv40–iv44)). Thus there are dimensions other than symptom reduction that relate to patient satisfaction in GORD.

**(4.5) As patient satisfaction is multidimensional, questions related to these dimensions and disease focused questions are useful to evaluate different aspects of treatment** (nature of evidence: D).

*Strength of recommendation:* agree strongly, 14%; agree, reservation, 86%; disagree, reservation, 0%; disagree strongly, 0%.

Indirect evidence for this comes from primary care studies which suggest that there are a number of dimensions to patient satisfaction.<sup>134–137</sup> Studies that address patient satisfaction therefore require evaluation of all of these dimensions, and also need disease specific outcome measures to determine the outcome of treatment.

*Editorial comment.* This vote emphasises the importance of measuring the many dimensions of patient satisfaction and also highlights the need for disease specific measures of clinical outcome.

**Are patients satisfied with current therapy for reflux disease?**

**(4.6) Absence of symptoms is a major determinant of patient satisfaction with therapy** (nature of evidence: D).

*Strength of recommendation:* agree strongly, 11%; agree, reservation, 18%; disagree, reservation, 64%; disagree strongly, 7%.

There is a lack of evidence to support this proposition. Absence of symptoms is paralleled by improved quality of life, and patient willingness to pay is higher for absence rather than reduction of symptoms.<sup>138</sup> However, there is a weak relationship between reduction of symptoms and patient satisfaction (Revicki<sup>133</sup> in this supplement (see page iv40–iv44)). The proposition was therefore rejected by the majority of participants.

*Editorial comment.* Although there is a correlation between reduction of symptoms and satisfaction, the correlation is poor because satisfaction measures other dimensions of care that are unrelated to symptom reduction. Patient satisfaction alone is therefore not a substitute for determining the absence of symptoms and vice versa.

**(4.7) In primary care, more than one third of patients are somewhat dissatisfied with current prescription medical therapy** (nature of evidence: C).

*Strength of recommendation:* agree strongly, 9%; agree, reservation, 86%; disagree, reservation, 5%; disagree strongly, 0%.

Patient satisfaction with outcome of therapy is a function of symptom reduction rather than healing of oesophagitis. Approximately two thirds of reflux oesophagitis patients treated with PPIs have abolition of symptoms while rates of symptom reduction are generally lower in studies of endoscope negative reflux disease. As there is no good correlation between symptom response and patient satisfaction, this may not be directly relevant to the proposition. A single study by Crawley and Schmitt, based on a cross sectional survey of approximately 20 000 chronic heartburn sufferers,<sup>132</sup> lends some support to the proposition. Of the 11 600 respondents, less than 60% were "totally satisfied with treatment" but not all the respondents were in primary care.

*Editorial comment.* The causes of dissatisfaction have not been studied and may include the cost of therapy and the

difficulty experienced in obtaining effective therapy in managed care. There are no validated tools that can be used in this setting and acquiescence bias is a potential confounding factor. The Crawley-Schmitt study<sup>132</sup> is interesting because it shows a difference between H<sub>2</sub> receptor antagonists and PPIs. Confounding factors should be similar in the two groups but access to PPI therapy is more difficult than to H<sub>2</sub> receptor antagonists in USA managed care settings.

**(4.8) Patients with reflux disease taking PPIs are more satisfied than patients taking H<sub>2</sub> receptor antagonists** (nature of evidence: C).

**Strength of recommendation:** agree strongly, 15%; agree, reservation, 65%; disagree, reservation, 19%; disagree strongly, 0%.

The superiority of symptom control with PPIs compared with H<sub>2</sub> receptor antagonists is well established although the poor correlation between symptom response and patient satisfaction may mean that this may not be directly relevant to the proposition. The Crawley and Schmitt cross sectional survey<sup>132</sup> again lends some support for the proposition, as 58% of patients taking PPI therapy were "totally satisfied with treatment" compared with 45% taking H<sub>2</sub> receptor antagonists.

**Editorial comment.** The small number of workshop participants who disagreed with this proposition were uncertain if dissatisfaction rates in the H<sub>2</sub> receptor antagonist group were related to poor symptom control, managed care mandates on the choice of therapy, or other factors. There were reservations about the Crawley and Schmitt study<sup>132</sup> because of the limited amount of information on satisfaction that was sought and the lack of data on the underlying disease (subjects were recruited from a pharmacy database).

How important are patient expectations in determining patient satisfaction?

**(4.9) Patient expectations need to be evaluated and discussed before embarking on therapy** (nature of evidence: B).

**Strength of recommendation:** agree strongly, 76%; agree, reservation, 16%; disagree, reservation, 8%; disagree strongly, 0%.

**(4.10) Patient expectations may need to be modified before embarking on therapy** (nature of evidence: D).

**Strength of recommendation:** agree strongly, 75%; agree, reservation, 21%; disagree, reservation, 4%; disagree strongly, 0%.

Patient satisfaction relates to how well their expectations are met. Indirect evidence of the impact on satisfaction of modifying expectation comes from a study of parents attending acute paediatric care who had a pre-visit desire for antibiotics to be prescribed.<sup>133</sup> When this expectation was discussed with parents, and information provided that the expectation might not be appropriate at that point in time, parent satisfaction was greater after the physician encounter in which antibiotics were not prescribed. These data suggest that patients may have medically incorrect expectations based on poor information. If these are not anticipated, discussed, and modified, patient satisfaction may be poor although medical treatment may be entirely appropriate. The recommendations in these two propositions are good for clinical practice. Care is needed in the conduct of randomised clinical trials of different treatment modalities to ensure that patient satisfaction results do not reflect improper expectations.

**Editorial comment.** Recent studies on surgery<sup>131</sup> suggest that patients with GORD undergoing surgery have incorrect expectations of the potential outcome. This vote reflects the importance of evaluating and addressing patient expectations.

**(4.11) Measurements of patient satisfaction have not been given adequate emphasis in the evaluation of drug therapy of reflux disease** (nature of evidence: B).

**Strength of recommendation:** agree strongly, 52%; agree, reservation, 44%; disagree, reservation, 4%; disagree strongly, 0%.

Of 152 articles identified in the systematic review by Sharma *et al* of outcome measures in reflux disease, only three randomised clinical trials (2%) measured patient satisfaction (Sharma and colleagues' in this supplement (see page iv58–iv65)). Where assessments have been made, they have not been adequate or validated.<sup>132–140</sup> This again underlines the need for validated instruments to measure patient satisfaction in GORD.

**Editorial comment.** This vote reflects the desire of most physicians to have a satisfied patient. Unfortunately, there are no validated instruments to perform such measurements at the present time.

Approximately half of the participants disagreed with the proposition that, in clinical trials, a validated measure of patient satisfaction with heartburn control is an important outcome measure for evaluation of long term treatment (proposition 2.14), largely because no validated instrument exists. However, this clouds the issue that multidimensional validated satisfaction scales are needed and that, when available, they will be of value. This was confirmed by broad acceptance of a subsequent proposition (4.12).

**(4.12) A valid and responsive treatment satisfaction scale should be used to assess secondary outcomes in clinical trials in GORD.**

**Strength of recommendation:** agree strongly, 59%; agree, reservation, 33%; disagree, reservation, 7%; disagree strongly, 0%.

**(4.13) There is a virtual absence of rigorous evaluation of patients' satisfaction with antireflux surgery and other physical antireflux therapies** (nature of evidence: B).

**Strength of recommendation:** agree strongly, 81%; agree, reservation, 19%; disagree, reservation, 0%; disagree strongly, 0%.

The Visick and modified Visick classifications have dominated the literature although they were designed for gastric ulcer surgery. They have not been validated in GORD and there is no uniform evaluation and no independent observer, as patients' satisfaction may often be assessed by the physician who performed the surgical procedure, which introduces a strong acquiescence bias. Global measures of patient satisfaction have not included a rigorous assessment of clinical outcomes.

**Editorial comment.** This vote reflects the need for patient satisfaction outcomes to be considered along with functional and clinical outcomes in GORD. Patient satisfaction is a limited and secondary measure of the outcome of surgery in GORD, and must be considered with other outcome measures, such as symptom reduction, side effects, etc.

**(4.14) Patient satisfaction is a useful measure for the evaluation of treatment algorithms developed by funders of health care** (nature of evidence: B).

**Strength of recommendation:** agree strongly, 11%; agree, reservation, 52%; disagree, reservation, 30%; disagree strongly, 7%.

Funders of health care may have a different agenda to patients. Switching of PPI maintenance therapy in GORD patients in a Veteran's Administration health care system resulted in significant cost savings but the majority of patients preferred the original PPI.<sup>141</sup> While patient satisfaction may be one useful measure for the evaluation of treatment algorithms, provided it can be measured adequately, it is not the only aspect to be taken into account, and its hierarchy in relation to other aspects is currently unclear. However, there may be treatment algorithms put forward by

health care providers where patient satisfaction is the only way of addressing them.

**Editorial comment.** The split vote reflects the fact that patient satisfaction may be too general a measure of a treatment algorithm, and that it may overemphasise the process of care. The lack of a validated instrument and absence of data correlating this measure with clinical outcome were causes for concern. Patient satisfaction data could be misused to drive less expensive and less effective therapy.

(4.15) *From the patient's perspective, the ideal outcome of therapy is the abolition of all symptoms, without the introduction of new ones from the therapy itself* (nature of evidence: E).

**Strength of recommendation:** agree strongly, 21%; agree, reservation, 71%; disagree, reservation, 7%; disagree strongly, 0%.

Absence of symptoms is paralleled by improved quality of life, and patient willingness to pay is higher for absence rather than reduction of symptoms.<sup>138</sup> However, these studies do not directly address the proposition, which was accepted based on expert opinion.

**Editorial comment.** While intuitive, this aspect of measurement has been neglected in many studies of surgery or endoscopic therapy. The impact of side effects that develop after the procedure can have a profound impact on quality of life<sup>139</sup> that needs to be considered in the overall evaluation of the treatment modality.

#### Future directions for research

Several areas of future research were identified. There is a pressing need for validated instruments that measure patient satisfaction. There is a need to measure patient expectations of GORD therapy, and to determine if patient expectations can be modified to adjust to the realities of the treatment available (for example, patients may desire a cure but may have to settle for maintenance therapy). Studies on surgical and endoscopic intervention have used the most rudimentary measures of patient satisfaction, and the development of a multidimensional disease specific instrument is a critical need to allow evaluation of these therapies.

#### Authors' affiliations

J Dent, Department of Gastroenterology, Hepatology, and General Medicine, Royal Adelaide Hospital, Adelaide, Australia

D Armstrong, Division of Gastroenterology, McMaster University Medical Centre, Hamilton, Canada

B Delaney, P Moayyedi, Department of Primary Care and General Practice, University of Birmingham, Birmingham, UK

N J Talley, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, USA

N Vakil, University of Wisconsin Medical School, Milwaukee, USA

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CME

# The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus

Nimish Vakil, M.D., F.A.C.G.,<sup>1</sup> Sander V. van Zanten, M.D.,<sup>2</sup> Peter Kahrilas, M.D.,<sup>3</sup> John Dent, M.D.,<sup>4</sup> Roger Jones, M.D.,<sup>5</sup> and the Global Consensus Group

<sup>1</sup>University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin and Marquette University College of Health Sciences, Milwaukee, Wisconsin; <sup>2</sup>Dalhousie University, Halifax, Nova Scotia, Canada;

<sup>3</sup>Northwestern University, Chicago, Illinois; <sup>4</sup>University of Adelaide, Adelaide, Australia; and <sup>5</sup>Kings College, London, United Kingdom

- OBJECTIVES:** A globally acceptable definition and classification of gastroesophageal reflux disease (GERD) is desirable for research and clinical practice. The aim of this initiative was to develop a consensus definition and classification that would be useful for patients, physicians, and regulatory agencies.
- METHODS:** A modified Delphi process was employed to reach consensus using repeated iterative voting. A series of statements was developed by a working group of five experts after a systematic review of the literature in three databases (Embase, Cochrane trials register, Medline). Over a period of 2 yr, the statements were developed, modified, and approved through four rounds of voting. The voting group consisted of 44 experts from 18 countries. The final vote was conducted on a 6-point scale and consensus was defined *a priori* as agreement by two-thirds of the participants.
- RESULTS:** The level of agreement strengthened throughout the process with two-thirds of the participants agreeing with 86%, 88%, 94%, and 100% of statements at each vote, respectively. At the final vote, 94% of the final 51 statements were approved by 90% of the Consensus Group, and 90% of statements were accepted with strong agreement or minor reservation. GERD was defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The disease was subclassified into esophageal and extraesophageal syndromes. Novel aspects of the new definition include a patient-centered approach that is independent of endoscopic findings, subclassification of the disease into discrete syndromes, and the recognition of laryngitis, cough, asthma, and dental erosions as possible GERD syndromes. It also proposes a new definition for suspected and proven Barrett's esophagus.
- CONCLUSIONS:** Evidence-based global consensus definitions are possible despite differences in terminology and language, prevalence, and manifestations of the disease in different countries. A global consensus definition for GERD may simplify disease management, allow collaborative research, and make studies more generalizable, assisting patients, physicians, and regulatory agencies.

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## INTRODUCTION

A number of guidelines and recommendations for the diagnosis and management of gastroesophageal reflux disease (GERD) have been published in different countries, but a universally accepted definition of GERD and its various symptoms and complications is lacking (1-9). Reflux symptoms are common in primary care and GERD is frequently diagnosed based on symptoms alone, but there is no consensus on the distinction of GERD from dyspepsia, so that these terms may lead to confusion in primary care settings. This

has led some authorities to combine these entities in primary care management strategies (10). There is also uncertainty about the extraesophageal manifestations of GERD, coupled with an expanding list of putative extraesophageal disorders, resulting in both over- and underdiagnosis of the disease. Finally, the definition of Barrett's esophagus varies in different regions of the world, causing confusion in the assessment of risk and the appropriate use of surveillance.

The aim of this international Consensus Group was to develop a global definition and classification of GERD, using rigorous methodology, that could be used clinically by primary care physicians and that embraces the needs of

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physicians, patients, researchers, and regulatory bodies from different parts of the world.

## METHODS

A modified Delphi process was used to develop the consensus definition of GERD (11–13). The Delphi process is a method for developing consensus that has been used for complex problems in medicine and industry. A novel aspect of this endeavor was the combination of the principles of evidence-based medicine, supported by systematic literature reviews, with the Delphi process. A key element of the Delphi process is the use of anonymous voting, which allows a change of views from a previously held position without embarrassment, together with controlled feedback regulated by a nonvoting chairman that prevents the process from being hijacked by a vocal minority. Systematic literature reviews were chosen to support the evidence base as this orientates the consensus process away from clinical opinion to methodologically sound evidence. Multiple iterations of the statements that make up the definition and classification were created until consensus was reached.

The principal steps in the process were: (1) Selection of the Consensus Group and development of draft statements by a Working Group; (2) Systematic literature reviews to identify the evidence to support each statement; (3) Grading of the evidence; (4) Voting discussion and repeated anonymous voting on a series of iterations of the statements until a consensus was reached. Each of these steps is described in more detail below.

### *Consensus Group Selection*

Members of the Consensus Group were selected using several criteria:

1. Demonstrated knowledge/expertise in GERD by publication/research or participation in national or regional GERD consensus guidelines or an interest in guideline development and dissemination.
2. Geographical considerations: individuals who met the criteria under (1) were then invited to provide broad representation of different regions of the world (North America, South America, Asia, Europe, Australia) that have differences in prevalence and manifestation.
3. Diversity of views and expertise related to GERD (including experts in Barrett's esophagus, surgeons, and primary care physicians).

The Consensus Group was led by a nonvoting chairman (NV). The Working Group, who are the primary authors of this article, developed the initial statements and prepared and reviewed the evidence to support the statements that were presented to the Consensus Group. The Consensus Group, which included the Working Group, consisted of 44 experts from 18 countries: Argentina, Australia, Belgium, Brazil, Canada,

China, Denmark, France, Germany, Hong Kong, Italy, Japan, Mexico, Netherlands, Peru, Sweden, United Kingdom, and the United States.

### *Systematic Searches*

Systematic literature reviews, with defined inclusion and exclusion criteria, were conducted to identify and grade the available evidence to support each statement. Literature searches were conducted of English language publications in Medline, Embase, and the Cochrane trials register, in human subjects from 1980 onwards. Searches of meeting abstracts (American College of Gastroenterology, American Gastroenterological Association, British Society of Gastroenterology, United European Gastroenterology Week) and review articles were limited to the preceding 2 yr. A number of search strings were used that are too numerous to list in the article. A complete list of the search strings may be obtained by communicating with the lead author of this article. Due to the large number of citations retrieved on each of the topics, the primary reviewer reviewed each of the abstracts and selected articles and meeting abstracts for further review. The review was qualitative and the primary reviewer reached an assessment on the grade assigned to the statement that was then reviewed in the Working Group. Quantitative meta-analyses were not performed. The references cited in this article are a fraction of the articles reviewed in each area and were selected to amplify the statements and the discussion in the Working Group.

### *Grades of Evidence*

Assignment of the grade of evidence for each statement, where applicable, employed the GRADE system, which takes into account the type of evidence while increasing or decreasing the grade depending on the quality of the study and data (14). The final grade provides a practical indication of the likely impact of further research on confidence in the estimate of effect. The grading of evidence is as follows:

- High: Further research is unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is likely to have an important impact on our confidence in the estimate of effect and is very likely to change the estimate.
- Very low: Any estimate of effect is uncertain.

An initial assessment of grade was made by the primary reviewer of the topic from within the Working Group. The assigned grade was then discussed within the Working Group and a final determination of grade was made. Assignment of grade was not voted upon in the broader Consensus Group. A grade of not applicable was chosen for definitions or statements that cannot be influenced by research. For

example a cluster of symptoms that is defined as a syndrome is an arbitrary designation and cannot be altered by research.

### Voting

The entire process lasted 2 yr and the Consensus Group voted on four iterations of the statements. Between each of the four votes, statements were revised by the Working Group based on feedback from the Consensus Group and additional literature reviews. All votes were anonymous.

1. A first vote (baseline) was conducted for the entire Consensus Group electronically (by e-mail), without explanation or justification of the statements, and the results were collated (Vote 1). Feedback on the statements was solicited.
2. A meeting of the entire Consensus Group was held to discuss suggested modifications based on feedback from the first vote and to review and discuss the evidence to support specific statements. Subsequently, a second vote was held, using electronic keypads to ensure anonymity (Vote 2).
3. Focus subgroups were created within the Consensus Group to address controversies in Barrett's esophagus and extraesophageal syndromes. Statements were again revised, this time with input from the focus subgroups. A third electronic vote was conducted by e-mail (Vote 3).
4. A final Consensus Group meeting was held and the complete results of the previous votes were reviewed, followed by an open discussion of all statements, including focused presentations on those statements where there was still lack of consensus. This culminated in the fourth and final vote, using keypads (Vote 4).

Regulatory agencies were invited to the initiative and the European Medicines Agency was represented by a nonvoting observer at the final Consensus Group meeting.

For the first two votes, a simple 2-point scale (agree/disagree) was used in order to rapidly identify areas where consensus/lack of consensus existed. For the third and fourth votes, a 6-point Likert scale was used: 1, agree strongly (A+); 2, agree with minor reservation (A); 3, agree with major reservation (A-); 4, disagree with major reservation (D-); 5, disagree with minor reservation (D); 6, disagree strongly (D+). Agreement with a statement (A+, A, or A-) by two-thirds (*i.e.*,  $\geq 67\%$ ) of the group was defined *a priori* as consensus. The level of agreement in the final vote is given for each statement, expressed as the percentage vote at each point on the Likert scale.

### Funding Sources

The process was funded by an unrestricted grant from Astra-Zeneca Research and Development. The European Medicines Agency was responsible for the costs of their observer.

### Endorsement by the World Organization of Gastroenterology

The final document was endorsed by the World Organization of Gastroenterology (WGO-OMGE) as "an important development in a critical area of gastroenterology worldwide." "Montreal" is in the title because the results of the study were first presented at the World Congress of Gastroenterology in Montreal.

## RESULTS AND DISCUSSION

### Overview of the Voting on Statements

A total of 57 statements were presented for the baseline Vote 1 and, following discussion of the supporting evidence, for Vote 2. The statements were subsequently revised and consolidated, providing 53 statements for Vote 3. Further discussion and modification at the final Consensus Group meeting resulted in 51 statements for the final Vote 4.

The level of consensus increased with each round of voting, with a high level of consensus in the fourth and final vote (Fig. 1). At each of the four votes, there was consensus (agreement by  $\geq 67\%$  of the group) on 86%, 88%, 94%, and finally 100% of statements, respectively. Over 90% of the group agreed with 94% (48) of the 51 final statements. Moreover the strength of agreement was very high by the final vote, as illustrated by the average percentage vote across the final 51 statements at each level of the 6-point Likert scale (Table 1). Following the final vote it became apparent that one statement had become redundant as it was already addressed in a preceding statement. Consequently, statements and accompanying commentary are given for 50 rather than 51 statements.

### Voting on the Process and Sponsor Influence

Anonymous votes were also obtained on the Delphi process and the influence of the sponsor on the outcome. Ninety percent of participants agreed that the voting process was fair and that they had a chance to input adequately. Ninety-two

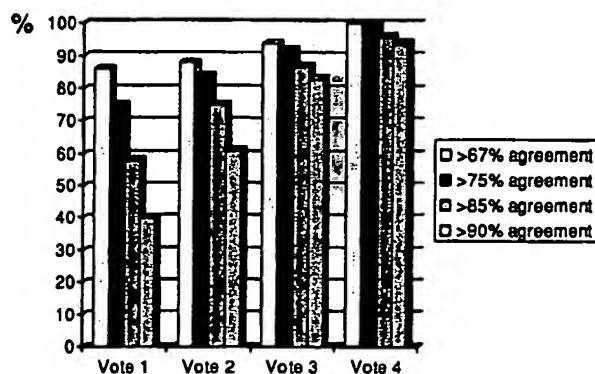


Figure 1. Percentage of statements at each level of agreement at each vote.

**Table 1.** The Average Percentage for the Final Vote, Across the Final 51 Statements, at Each Level of the 6-Point Scale

|    |                                 |       |
|----|---------------------------------|-------|
| A+ | Agree strongly                  | 67.2% |
| A  | Agree with minor reservation    | 23.4% |
| A- | Agree with major reservation    | 6.7%  |
| D- | Disagree with major reservation | 1.5%  |
| D  | Disagree with minor reservation | 0.9%  |
| D+ | Disagree strongly               | 0.3%  |

percent of the participants agreed that the sponsor had not, in any way, influenced their voting

### THE GLOBAL DEFINITION OF GERD.

#### 1. GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications

Level of agreement: A+, 81%; A, 14%; A-, 5%; D-, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

We used the general definition of a disease to arrive at a definition of GERD, *i.e.*, a disease is defined as a morbid entity characterized usually by at least two of these criteria: (1) recognized etiologic agent(s); (2) identifiable group of signs and symptoms; (3) consistent anatomic alterations (15). We considered a number of descriptive terms before choosing "troublesome" because it satisfactorily describes the negative aspects of the symptoms from a patient's standpoint, allows itself to be translated into a number of languages, and recognizes the variability in how symptoms impact individual patients. The group recognized that the characteristic symptoms of GERD are retrosternal burning (often labeled heartburn) and regurgitation, and the most common manifestation of esophageal injury is reflux esophagitis (16-18).

The language of the definition is designed to allow asymptomatic patients with complications such as Barrett's esophagus to be included in the case-definition of GERD, and be independent of technology used to achieve a diagnosis. For example, patients may be diagnosed based on typical symptoms alone or on the basis of investigations that demonstrate reflux of stomach contents (*e.g.*, pH testing, impedance monitoring) or the injurious effects of the reflux (endoscopy, histology, electron microscopy), in the presence of typical or atypical symptoms or complications (19, 20). The new definition also recognizes that the refluxate causing symptoms may be weakly acidic or gaseous and these patients also meet the case-definition of GERD.

**Classification of the manifestations of GERD:** There is a conceptual change in the classification of GERD-related disease manifestations in that it is presented as a set of syndromes (Fig. 2). A syndrome has been defined as the aggregate of symptoms and signs associated with any morbid process, and constituting the picture of the disease (15). In preliminary voting there was over 90% agreement with this definition of a syndrome and with the syndrome-based ap-

proach to the definition of GERD, reflecting the clinical reality that patients with GERD may present in a number of ways.

We divided the manifestations of GERD into esophageal and extraesophageal syndromes, with extraesophageal syndromes divided into established and proposed associations (Fig. 2). Uninvestigated patients with esophageal symptoms but without evidence of esophageal injury are considered to have esophageal symptomatic syndromes while patients who do have demonstrable injury are considered to have esophageal syndromes with esophageal injury. The rationale for this terminology was that clinicians may need to define and classify patients based on differing amounts of information. In primary care, for example, many patients do not undergo endoscopy to make a diagnosis of GERD and many patients who do, have no abnormalities at endoscopy. The proposed consensus definition therefore allows symptoms to define the disease but permits further characterization if mucosal injury is found. The concept of nonerosive reflux disease is preserved in the typical reflux syndrome without esophageal injury, while reflux esophagitis falls under the category of esophageal syndromes with esophageal injury. The terms ENRD (endoscopy negative reflux disease) and NERD (nonerosive reflux disease), while recognized in the statements, were not used in the classification scheme as they are based entirely on a diagnostic test (endoscopy) that may not be utilized in many patients and which is itself likely to evolve with new instruments and techniques, *e.g.*, magnification endoscopy.

Within the category of esophageal symptomatic syndromes, the reflux chest pain syndrome is listed separately recognizing a group of patients who may present with chest pain without the associated symptoms of the typical reflux syndrome or with pain overshadowing typical reflux symptoms. Within the syndromes with esophageal injury are the well-recognized aspects of mucosal injury including reflux esophagitis, stricture, Barrett's esophagus, and adenocarcinoma. The term reflux esophagitis was preferred over erosive esophagitis because it is increasingly recognized that the demonstration of esophageal erosions may vary with the technology being used. For example, patients with no erosions at endoscopy may prove to have erosions using specialized techniques such as magnification endoscopy. Similarly, patients with no abnormalities at endoscopy may have abnormalities on histological examination at electron microscopy such as dilated intercellular channels (21). A major advantage of this new terminology and classification is that it is likely to endure despite changes in technology that improve our ability to detect esophageal injury.

#### 2. GERD is common and its prevalence varies in different parts of the world

Level of agreement: A+, 84%; A, 14%; A-, 2%; D-, 0%; D, 0%; D+, 0% (*Grade: High*)

Population-based studies suggest that GERD is a common condition with a prevalence of 10-20% in Western Europe



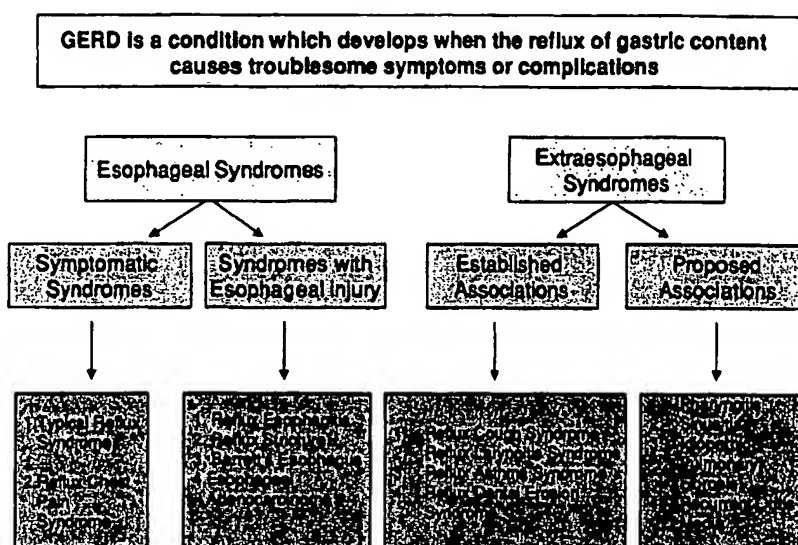


Figure 2. The overall definition of GERD and its constituent syndromes.

and North America (22, 23). The prevalence rates in South America (10%) and Turkey (11.9%) are similar to European countries (24, 25). In Asia, the prevalence has been variably reported but is generally lower. Chen *et al.* reported that the prevalence of heartburn occurring weekly was 6.2% while Wong *et al.* found a lower prevalence of 2.3% (26, 27). A longitudinal study from Singapore suggests that the prevalence of GERD is increasing with an increase in the prevalence of GERD symptoms from 5.5% of the population in 1994 to 10.5% in 1999 (28). Few population-based studies are available from Africa but the available data suggest that in sub-Saharan Africa, GERD and its complications are rare (29).

**3. Symptoms related to gastroesophageal reflux become troublesome when they adversely affect an individual's well-being**

Level of agreement: A+, 70%; A, 30%; A-, 0%; D-, 0%; D, 0%; D+, 0% (Grade: Not applicable)

**4. Reflux symptoms that are not troublesome should not be diagnosed as GERD**

Level of agreement: A+, 56%; A, 28%; A-, 9%; D-, 5%; D, 2%; D+, 0% (Grade: Not applicable)

Inherent in the overall definition (Statement 1) is the need to define when symptoms reach a threshold at which they are troublesome to the patient, given that occasional heartburn is common and does not, by itself, constitute a disease. This is addressed by these two statements, in which the word "troublesome" was chosen from a number of other possibilities, such as "bothersome," "troubling," "annoying," etc., following an exercise to determine comprehensibility in several languages and the accuracy of back translation. Quality of life as measured by generic and disease-specific quality of life instruments deteriorates as the severity of GERD symptoms increases (30–32). However, quality of life can be affected by

a number of parameters and cannot be readily measured in clinical practice. In contrast, well-being is a patient-centered end point that is easily understood and is therefore used in the definition of GERD rather than quality of life.

An important caveat to the statement on nontroublesome reflux symptoms is that patients may be asymptomatic and may still have underlying complications such as reflux esophagitis or Barrett's esophagus and thereby meet the criteria for the case-definition of GERD. (Statement 1).

**5. In population-based studies, mild symptoms occurring 2 or more days a week, or moderate/severe symptoms occurring more than 1 day a week, are often considered troublesome by patients**

Level of agreement: A+, 44%; A, 46%; A-, 5%; D-, 5%; D, 0%; D+, 0% (Grade: Moderate)

**6. In clinical practice, the patient should determine if their reflux symptoms are troublesome**

Level of agreement: A+, 60%; A, 35%; A-, 5%; D-, 0%; D, 0%; D+, 0% (Grade: Not applicable)

The group felt that population-based studies that attempt to define a threshold at which symptoms become troublesome were useful in planning large treatment trials or epidemiologic studies but they were of limited utility in clinical practice. The Consensus Group therefore concluded that in clinical practice the determination of whether symptoms were troublesome should be patient-centered without the use of arbitrary cutoffs for frequency and duration. Data from population-based studies are limited but provide a glimpse of the effects of GERD in a population. In a population-based study in Sweden, symptoms of heartburn or upper abdominal pain that were mild or worse were associated with a clinically meaningful reduction in well-being (33). Data for symptom frequency come from a population-based study of two communities in northern Sweden. (34). Mild symptoms on 2 or

more days a week were associated with a significant reduction in quality of life measured by a disease-specific instrument (QOLRAD). Similar data have been reported from a cohort in the United States (35).

**ESOPHAGEAL SYNDROMES: SYMPTOMATIC.** These syndromes are defined by the constellation of symptoms and may or may not be characterized by further diagnostic tests.

*Typical reflux syndrome:* The typical reflux syndrome is defined by the presence of troublesome heartburn and/or regurgitation. Patients may also have other symptoms such as epigastric pain or sleep disturbance.

**7. Heartburn is defined as a burning sensation in the retrosternal area (behind the breastbone)**

Level of agreement: A+, 79%; A, 21%; A—, 0%; D—, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

Heartburn is a term that translates poorly into many languages, so that various terms, that are not literal translations of heartburn but are used by patients as well as doctors, are employed in many countries. A definition is needed to provide a clear description of this symptom. Early iterations of this statement also included a substernal element (defined as the central part of the upper abdomen immediately below the breastbone area), but this was removed because of possible confusion over the location of the burning sensation, and the qualifier was added to the retrosternal location in the statement.

**8. Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx**

Level of agreement: A+, 65%; A, 28%; A—, 7%; D—, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

Regurgitation has been variably described in most clinical trials and epidemiological studies on GERD. The definition developed by the Consensus Group is sufficiently rigorous for future epidemiological and clinical research, although this consensus definition was arrived at after considerable debate. Some members initially felt that regurgitation included the perception of gastric content entering the esophagus while others felt that it required the gastric content to enter the mouth or hypopharynx. After much discussion, the consensus statement (above) was agreed upon.

**9. Heartburn and regurgitation are the characteristic symptoms of the typical reflux syndrome**

Level of agreement: A+, 95%; A, 5%; A—, 0%; D—, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

Studies in this area are limited by the lack of a gold standard for the diagnosis of GERD. We identified 40 studies reporting the prevalence of heartburn in GERD. Among these, however, we were unable to find a single study that examined unselected individuals with heartburn and correlated the findings with both endoscopy and pH monitoring, or any that calculated the sensitivity, specificity, and predictive values of heartburn for an endoscopic and pH-metry diagnosis of

GERD. The much-cited study by Klauser *et al.*, in which a sensitivity of 78% and specificity of 60% for heartburn were reported, was conducted on a highly selected population referred for pH monitoring (16). In patients who previously had antireflux surgery, Eubanks and colleagues found that heartburn was the only symptom to have a significant correlation with acid exposure, and had a positive predictive value of 43% and a negative predictive value of 82%, with overall accuracy of 78% (36). There has been some discussion of the value of "dominant heartburn" in the diagnosis of GERD. A study from the United Kingdom showed that patients with "dominant heartburn" have a little over 50% chance of having GERD as defined by 24-h esophageal pH studies (37). Various studies of patients with GERD, including those entered into large proton pump inhibitor (PPI) trials, indicate that the prevalence of heartburn and regurgitation 75–98% and 48–91%, respectively (38–41).

Our literature search relating to the etiology and management of regurgitation revealed variability in assumptions on the relationship of heartburn and regurgitation. Of the 300 references examined, 163 related to adult GERD and demonstrated that, even in the most recent studies, heartburn and regurgitation are generally described together or as "heartburn or regurgitation" (42). This suggests that there is a belief that each symptom is equally and independently typical of GERD. This view is also held for Asian populations (43). The evidence for this belief comes mostly from the description of symptoms in patients with GERD entered into therapeutic trials of acid suppression, although even in trials the two characteristic GERD symptoms tend to be lumped together, or use heartburn scores as the principal end point (44). As discussed above, much of the variability in this area is attributable to lack of consistency in the definition of heartburn and regurgitation. It is hoped that this will be improved by adoption of the definitions in preceding statements.

**10. Gastroesophageal reflux is the most common cause of heartburn**

Level of agreement: A+, 88%; A, 12%; A—, 0%; D—, 0%; D, 0%; D+, 0% (*Grade: High*)

Heartburn has many causes, but of the 34 studies identified, none were able to accurately describe the frequencies of acid and nonacid causes of heartburn in unselected patients. Indirect evidence for acid causing most heartburn comes from the multitude of therapeutic trials of acid suppression in GERD. The relationship between acid suppression and relief of heartburn is indirectly demonstrated by trials of acid suppression. A recent Cochrane meta-analysis of short-term treatment trials in GERD showed that the relative risk (RR) of relief from heartburn increased with greater degrees of acid suppression: prokinetic agents (RR 0.86, CI 0.73–1.01), H<sub>2</sub>-receptor antagonists (RR 0.77, CI 0.60–0.99), PPIs (RR 0.37, CI 0.32–0.44) (45). As suppression of acid is very effective in alleviating heartburn, this provides indirect evidence for the association between acid reflux and heartburn.



**11. Heartburn can have a number of nonreflux related causes. The prevalence of these is unknown**

Level of agreement: A+, 65%; A, 31%; A-, 2%; D-, 0%; D, 2%; D+, 0% (*Grade: Moderate*)

Most studies examining the relevance of nonacidic or weakly acidic causes of heartburn have been conducted in patients with persistent/refractory symptoms, in selected secondary or tertiary care populations, or in postoperative patients (46). The importance of heartburn in this setting has often been emphasized and discussed but infrequently quantified (47, 48). A careful study of poorly responsive heartburn patients, using pH monitoring and Bilitec monitoring during PPI therapy, found that duodenogastric reflux played a role in the genesis of symptoms (49). Using impedance and pH recordings, it has been found that gas reflux, with and without drops in pH, particularly in patients with reflux-attributed laryngeal lesions, coincided with symptoms (50). What remains unclear is the extent to which nonacid or weakly acid reflux plays a role in the genesis of GERD symptoms in untreated patients, although it is clear from these and other studies that acid reflux is far more common than nonacid reflux, but that this pattern changes when PPI treatment is initiated (51).

**12. The typical reflux syndrome can be diagnosed on the basis of the characteristic symptoms, without diagnostic testing**

Level of agreement: A+, 79%; A, 16%; A-, 5%; D-, 0%; D, 0%; D+, 0% (*Grade: Moderate*)

**13. Nonerosive reflux disease is defined by the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy**

Level of agreement: A+, 81%; A, 12%; A-, 7%; D-, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

Because the typical reflux syndrome is defined symptomatically, it can be diagnosed on the basis of a clinical history, without the need for diagnostic testing. This is supported by a recent systematic evaluation of approaches to symptom evaluation in GERD (52). Furthermore, patients with characteristic reflux symptoms but no esophageal injury at endoscopy meet the criteria of the typical reflux syndrome. The absence of visible erosions is reported in over 50% of patients presenting with reflux symptoms in primary care, but if their symptoms are troublesome, they have the typical reflux syndrome (53-57). These statements have a strong message for primary care physicians, faced with the need to make a clinical diagnosis and to minimize expensive investigation, and are supported by the meta-analysis of treatment trials referred to earlier (45).

**14. Epigastric pain can be the major symptom of GERD**

Level of agreement: A+, 49%; A, 28%; A-, 14%; D-, 2%; D, 7%; D+, 0% (*Grade: Moderate*)

Perfusion of dilute acid into the distal esophagus has been shown to cause epigastric pain, but there are few data on the prevalence of epigastric pain in reflux disease (58). Some au-

thors have suggested that most patients with pain or discomfort centered in the upper abdomen (dyspepsia) who respond to acid suppression have acid reflux when they undergo pH testing (59). In two large randomized controlled trials of acid inhibition in nonerosive reflux disease, 69% of patients had epigastric pain in addition to symptoms of heartburn (60). All patients had undergone endoscopy to rule out the presence of significant mucosal disease of the esophagus so that this is a selected population. Acid-suppressive therapy resolved heartburn and epigastric pain in these patients and there was a strong correlation between the resolution of heartburn and the resolution of epigastric pain. As most endoscopic tests in patients with epigastric pain do not reveal any significant abnormalities, studies such as these raise the question of whether the typical reflux syndrome is the principal cause of epigastric pain in nonulcer dyspepsia as well. A recent study has identified a subset of heartburn-negative functional dyspepsia patients, with moderate to severe epigastric pain, who also have pathological esophageal acid exposure (61).

**15. GERD is frequently associated with sleep disturbance**

Level of agreement: A+, 44%; A, 37%; A-, 15%; D-, 2%; D, 0%; D+, 2% (*Grade: Moderate, as fully published data are as yet limited*)

This statement is supported by a large general population survey that found that heartburn occurred during the sleep period in 25% of 15,314 respondents and also by surveys of patients with reflux disease that have reported a prevalence of sleep disturbance ascribed to heartburn and/or regurgitation ranging from 23% to 81% (62-66). Similar data come from clinical trials that examine sleep disturbance prior to the start of therapy for reflux disease (67-69). The methods used to assess sleep disturbance have varied from polysomnography to fully validated questionnaires and single questions of uncertain validity. The increase of interest in this area means that several important studies are not yet fully reported.

**16. Night-time heartburn and sleep disturbance reported by patients with GERD are substantially improved by PPI therapy or antireflux surgery**

Level of agreement: A+, 51%; A, 36%; A-, 11%; D-, 2%; D, 0%; D+, 0% (*Grade: Moderate, as fully published data are as yet limited*)

Therapeutic studies of reflux disease provide the most extensive data to support a causal link between reflux disease and sleep disturbance. One large scale placebo-controlled trial of acid suppression in reflux disease patients provides the most rigorous support of the statement (70). Other less well-controlled or smaller studies are also supportive (66-69, 71).

**17. Physical exercise may induce troublesome symptoms of GERD in patients who have no/minimal symptoms at other times (exercise-induced gastroesophageal reflux)**

Level of agreement: A+, 65%; A, 30%; A-, 5%; D-, 0%; D, 0%; D+, 0% (*Grade: Low*)

Symptoms of GERD can develop with physical exercise. Exercise-induced gastroesophageal reflux is a well-recognized condition, that has been studied in the laboratory and in controlled environments. However, little community-based or epidemiological data are presently available. Stationary cycling, running, and weight training can produce reflux in healthy volunteers (72). Experiments using graded exercise in athletes have revealed reductions in the duration, amplitude, and frequency of esophageal contractions, accompanied by increases in the number of gastroesophageal reflux episodes and the duration of acid exposure during exercise, particularly at the most intense levels of exercise (73, 74). These physiological changes appear to be dependent both on the nature of the exercise and its intensity. Similar results have been obtained in untrained subjects. More recently, these data have been replicated for other activities, although research in trained cyclists has suggested that the physical agitation and movement of the body may be more important than the exercise *per se* in producing these symptoms (75, 76). There appears to be no correlation between gastroesophageal reflux and exercise-induced bronchoconstriction or asthma (77). In a small study of 14 subjects with heartburn studied during exercise, only a minority of symptomatic episodes were associated with reflux episodes. Exercise worsened reflux by pH-metry, and PPI therapy decreased reflux episodes as measured by pH studies. However, symptoms improved only in patients with a symptom index > 50% (78). Exercise-induced gastroesophageal reflux is not characterized by any specific signs or complications. Furthermore, the important and potentially confusing links with exercise-induced chest pain and ischemic heart disease need to be borne in mind.

#### *Reflux chest pain syndrome:*

#### **18. Chest pain indistinguishable from ischemic cardiac pain can be caused by GERD**

Level of agreement: A+, 79%; A, 14%; A-, 7%; D-, 0%; D, 0%; D+, 0% (*Grade: High*)

#### **19. Gastroesophageal reflux can cause episodes of chest pain that resemble ischemic cardiac pain, without accompanying heartburn or regurgitation**

Level of agreement: A+, 74%; A, 19%; A-, 5%; D-, 2%; D, 0%; D+, 0% (*Grade: Moderate*)

We found 178 articles on "noncardiac chest pain" and GERD. Few were based in the community or in primary care, and these were generally of cross-sectional design. In a study using the general practice research database (GPRD), a cohort of 13,740 patients with new onset chest pain in 1996 was identified and compared with an age- and sex-matched sample of 20,000 nonchest pain patients (79). At 1-yr follow-up the odds ratio (OR) for a diagnosis of GERD was 3.0, for dyspepsia 2.7, and for peptic ulcer disease 3.0. The ORs for ischemic heart disease and heart failure were 14.9 and 4.7, respectively. Richards and colleagues in Glasgow showed that

in a large community sample of chest pain sufferers, with an overall prevalence of chest pain of approximately 15%, noncardiac pain was more common than angina in men and women in the more affluent social strata, but that the prevalence of cardiac pain exceeded that of noncardiac pain in both men and women in lower socioeconomic groups (80). A number of studies have reported population prevalences of noncardiac chest pain of up to 25% (81-83).

A more recent Australian population-based study found a prevalence of noncardiac chest pain of 32% in men and 39% in women (84). The prevalence of diagnosed ischemic heart disease was 7%, while heartburn and acid regurgitation were both significantly and independently associated. A study in Hong Kong, using similar methodology to Richards *et al.*, found a population prevalence of chest pain of 20.6%, and that GERD was present in 51% of subjects with noncardiac chest pain, which was also associated with higher levels of depression and anxiety (80, 85).

In their Swedish primary care follow-up study, Nilsson and colleagues examined 38,075 general practitioner consultations, of which 577 (1.5%) were for chest pain (86). Ischemic heart disease was diagnosed in 8% of these and excluded in 83%, of which the majority were thought to have a musculoskeletal cause. An esophageal cause was suspected in 10% although the nonischemic heart disease patients were not investigated by endoscopy or pH-metry. More research into the relationship between chest pain and GERD is necessary to clarify some of these issues.

#### **20. Esophageal motor disorders can cause pain that resembles ischemic cardiac pain by a mechanism separate from gastroesophageal reflux**

Level of agreement: A+, 77%; A, 23%; A-, 0%; D-, 0%; D, 0%; D+, 0% (*Grade: Moderate*)

#### **21. Gastroesophageal reflux is more frequently a cause of chest pain than esophageal motor disorders**

Level of agreement: A+, 77%; A, 21%; A-, 2%; D-, 0%; D, 0%; D+, 0% (*Grade: Moderate*)

The importance of gastroesophageal reflux, compared with esophageal motor disorders, in causing noncardiac chest pain is demonstrated both by analysis of treatment trials of acid suppression in noncardiac chest pain, summarized in a recent meta-analysis, and by the relative infrequency with which motor abnormalities are found in noncardiac chest pain, except when associated with significant dysphagia (87-89). In a study of 140 patients undergoing esophageal manometry for noncardiac chest pain, manometry was normal in 70% of patients and the most frequent abnormality was a hypotensive lower esophageal sphincter (61% of abnormal studies). Spastic motility disorders, such as nutcracker esophagus (10%), hypertensive lower esophageal sphincter (10%), and diffuse esophageal spasm (2%), were much less common (89).

# ESOPHAGEAL SYNDROMES: SYNDROMES WITH ESOPHAGEAL INJURY.

## 22. Esophageal complications of gastroesophageal reflux disease are reflux esophagitis, hemorrhage, stricture, Barrett's esophagus, and adenocarcinoma

Level of agreement: A+, 42%; A, 26%; A-, 16%; D-, 9%; D, 7%; D+, 0% (*Grade: High*)

In clinical practice, endoscopic esophagitis is seen in less than 50% of patients with typical GERD symptoms (90-93). Esophageal erosions, *i.e.*, reflux esophagitis, therefore represent the most common consequence of esophageal injury rather than the principal manifestation of GERD. Reflux esophagitis is the most common manifestation of esophageal injury. The advantage of the term reflux esophagitis is that it can be easily documented during endoscopy and provides an objective criterion for diagnosis. Healing of reflux esophagitis can also be used as a reliable end point for success of therapy and correlates well with improvement of symptoms. Indeed, the fact that acid inhibition heals reflux esophagitis supports the notion that it is a manifestation of GERD.

Esophagitis may also be found at histopathology. Microscopic changes of the esophageal mucosa can be present in patients who do not have endoscopically visible esophagitis but the reliability of histology in making a diagnosis of GERD has been questioned (94). Histological abnormalities include an increase in polymorphonuclear and mononuclear white cells, basal cell hyperplasia, and elongation of the papilla (95). Electron microscopic abnormalities, such as dilated intercellular spaces, have been described in nonerosive reflux disease (96).

Other less common complications of GERD are hemorrhage, stricture, Barrett's esophagus, and adenocarcinoma of the distal esophagus (97, 98). Bleeding due to GERD is rare and is mainly seen in patients who have esophageal ulcers (99). The other manifestations of esophageal injury listed above are addressed in more detail in subsequent statements.

### *Reflux esophagitis:*

## 23. Reflux esophagitis is defined endoscopically by visible breaks of the distal esophageal mucosa

Level of agreement: A+, 93%; A, 7%; A-, 0%; D-, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

Reflux esophagitis is diagnosed by endoscopy when visible breaks are seen in the esophageal mucosa at or immediately above the GE junction. Various classification systems have been published to grade the severity of endoscopic esophagitis. Over the last 10 yr the Los Angeles classification has gained general acceptance (100-102). There is strong evidence that visible breaks in the mucosa are the most reliable endoscopic sign of esophagitis (100-104). Other findings such as erythema at the GE junction or an irregular Z-line have proven not to be reliable findings for a diagnosis of reflux esophagitis (103, 104).

## 24. Mucosal breaks may be intermittently present in patients with the reflux esophagitis syndrome

Level of agreement: A+, 65%; A, 28%; A-, 5%; D-, 2%; D, 0%; D+, 0% (*Grade: Low*)

## 25. Over a 20-yr period, the severity of reflux esophagitis does not increase in most patients

Level of agreement: A+, 12%; A, 44%; A-, 37%; D-, 5%; D, 2%; D+, 0% (*Grade: Low*)

Data on the natural course of GERD are sparse. Few studies have specifically investigated whether severity of symptoms or severity of complications, especially reflux esophagitis, change over time. Large studies of the natural history of GERD are unlikely to be conducted, as the majority of patients will be treated for their symptoms. The available limited evidence suggests that the severity of GERD symptoms, both on and off treatment, does not change over time in most patients (91, 105-110). There is also evidence that in most patients GERD is a chronic condition and that symptoms will persist (105-110). Consequently many of these patients will require long-term treatment either continuously or intermittently. In this statement "a 20-yr period" was added because there are no published data beyond this time frame. It is likely that slow progression will occur in a proportion of patients. The data showing that older individuals have more severe esophagitis, and that the prevalence of complications such as Barrett's esophagus and cancer increases with age, support this notion (111). A very limited number of studies have evaluated whether endoscopic findings, such as presence or absence of reflux esophagitis or grade of esophagitis, are stable over time. A few studies suggest that mucosal breaks may be intermittently present in patients who were previously diagnosed with reflux esophagitis (105-107, 109). Similarly, reflux esophagitis will be seen in a proportion of patients in whom an earlier endoscopy did not reveal endoscopic abnormalities, suggesting that progression may take place at a slow rate in a subset of patients (105-107, 109). One problem that is frequently encountered in practice is that many patients are already receiving, or have recently received, treatment when they come for endoscopy. This will make it difficult to make definitive statements about whether the patient ever had reflux esophagitis.

## 26. Although heartburn frequency and intensity correlate with the severity of mucosal injury, neither will accurately predict the severity of mucosal injury in the individual patient

Level of agreement: A+, 65%; A, 21%; A-, 9%; D-, 5%; D, 0%; D+, 0% (*Grade: Moderate*)

Factors that predict the presence of esophagitis are the frequency and duration of reflux episodes, occurrence of day and night time reflux episodes, and the presence of a hiatus hernia (112-116). Although the frequency and intensity of symptoms have been shown to have a moderate correlation with severity of endoscopic findings in several studies, generally symptoms will not accurately predict what the endoscopic findings will be in an individual patient (93, 112-116). Furthermore, for elderly patients there are data to suggest that despite evidence of more severe esophagitis, the

intensity of heartburn symptoms was less when compared to younger patients (111). By relying on heartburn severity one may therefore underestimate the severity of esophagitis in elderly patients (111). Similarly, there is also some evidence that patients with Barrett's esophagus may report less frequent or less severe symptoms (117).

*Reflux stricture:*

27. A reflux stricture is defined as a persistent luminal narrowing of the esophagus caused by GERD

Level of agreement: A+, 93%; A, 7%; A-, 0%; D-, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

28. The characteristic symptom of a stricture is persistent troublesome dysphagia

Level of agreement: A+, 96%; A, 2%; A-, 2%; D-, 0%; D, 0%; D+, 0% (*Grade: High*)

29. Dysphagia is a perceived impairment of the passage of food from the mouth into the stomach

Level of agreement: A+, 84%; A, 11%; A-, 5%; D-, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

A reflux stricture can develop as a result of severe reflux disease, when inflammation results in narrowing of the esophageal lumen so that passage of food is impaired. This is seen in <5% of GERD patients (91). Usually patients who have a reflux stricture will complain of persistent and troublesome dysphagia. Often such patients will require endoscopic dilatation in addition to acid suppressive therapy to obtain improvement in dysphagia symptoms.

The term dysphagia should be limited to the sensation of impeded passage of solid food or liquids through the esophagus, while oropharyngeal dysphagia is difficulty with the movement of solids or liquids from the mouth into the esophagus, which is unrelated to GERD. Odynophagia is defined as painful swallowing and is a common symptom in infectious esophagitis (e.g., candida, herpes).

An important component of the new GERD definition is that symptoms are troublesome. Troublesome dysphagia is more related to solids than liquids. Nontroublesome dysphagia is common in GERD. In a combined analysis of 11,495 patients with erosive esophagitis, 37% reported dysphagia when a symptom checklist was used. Dysphagia resolved in most patients (83%) following treatment with a PPI (118).

30. Troublesome dysphagia is present when patients need to alter eating patterns or report food impaction

Level of agreement: A+, 75%; A, 19%; A-, 2%; D-, 2%; D, 2%; D+, 0% (*Grade: Not applicable*)

31. Dysphagia is troublesome in a small proportion of patients with GERD

Level of agreement: A+, 70%; A, 28%; A-, 2%; D-, 0%; D, 0%; D+, 0% (*Grade: Low*)

32. Persistent, progressive, or troublesome dysphagia is a warning symptom for stricture or cancer of the esophagus and warrants investigation

Level of agreement: A+, 88%; A, 10%; A-, 0%; D-, 0%; D, 2%; D+, 0% (*Grade: High*)

Troublesome dysphagia is present when patients need to alter their eating patterns or have symptoms of solid food getting impacted. Dysphagia is troublesome only in a minority of GERD patients. There is agreement that troublesome and worsening dysphagia, especially for solids, is an alarm symptom. It warrants investigation, as it could be indicative of more serious pathology, such as a peptic stricture or cancer of the esophagus. Recent reviews have confirmed that having dysphagia increases the risk (OR 3-4) of having an upper GI malignancy (119, 120).

*Barrett's esophagus:*

33. The term Barrett's esophagus is variably interpreted at the present time and lacks the clarity needed for clinical and scientific communication about columnar metaplasia of the esophageal mucosa

Level of agreement: A+, 63%; A, 19%; A-, 11%; D-, 7%; D, 0%; D+, 0% (*Grade: Not applicable*)

There is a universal agreement that the core component of all of the varying definitions of Barrett's esophagus is the partial replacement, from the gastroesophageal junction proximally, of esophageal squamous epithelium with metaplastic columnar epithelium. The term "Barrett's esophagus" is currently confusing and ambiguous because the spectrum of what is currently referred to as "Barrett's esophagus" ranges from some clinicians making this diagnosis solely on the basis of endoscopic appearances of any extent, to the requirement that intestinal-type esophageal columnar metaplasia be proven histologically before this diagnosis is made (121, 122). A recent study in clinical practice in Munich showed that the consistency of endoscopic and histological findings between an index endoscopy and one performed 2 yr later was poor, with similar results obtained in only one-third of patients (123). In patients in whom the endoscopy initially suggested Barrett's esophagus but the biopsy was not confirmatory of intestinal metaplasia, 42% of patients did not have Barrett's esophagus at endoscopy or on histology at a subsequent examination. Thus, there appears to be a variability in the endoscopic diagnosis of Barrett's esophagus as well. Some of these results may be explained by biopsy sampling error or the demonstration of gastric metaplasia at biopsy. These differing usages were acknowledged as a problem by the Consensus Group. At a recent workshop, 72% of the 18 physicians reviewing the data on Barrett's esophagus agreed that esophageal intestinal metaplasia documented by histology was a prerequisite for the diagnosis of Barrett's esophagus, while 16% had major reservations with this requirement for the definition and 12% rejected this concept (124). A subsequent study examining the conformity between practicing U.S. gastroenterologists and the workshop group found further disparities in opinion. Only 72% of practicing U.S. gastroenterologists agreed that intestinal metaplasia was a prerequisite for the diagnosis of Barrett's esophagus (125). These data suggest the notion that intestinal metaplasia is a

prerequisite for the diagnosis of Barrett's esophagus is not uniformly accepted even in the United States where this concept originated.

**34. Neither the frequency nor the severity of heartburn is useful for prediction of the presence, type, or extent of esophageal columnar metaplasia**

Level of agreement: A+, 84%; A, 12%; A-, 2%; D-, 0%; D, 2%; D+, 0% (*Grade: Moderate*)

The qualifier "useful" in this statement was taken to mean the ability to recognize individual patients with esophageal columnar metaplasia on the basis of heartburn severity and frequency alone. It was readily agreed that these criteria are not discriminatory (126-128). It has also been shown that 5.6-25% of older people free of troublesome heartburn have evidence of esophageal columnar metaplasia (19, 129). For patients with reflux disease, detailed analysis of factors such as age, gender, and duration and pattern of reflux symptoms can identify individuals at an increased risk of having esophageal columnar metaplasia (127, 128, 130).

**35. Endoscopically suspected esophageal metaplasia (ESEM) describes endoscopic findings consistent with Barrett's esophagus that await histological evaluation**

Level of agreement: A+, 72%; A, 24%; A-, 2%; D-, 0%; D, 2%; D+, 0% (*Grade: Not applicable*)

It was agreed that there should be a terminology that differentiates a purely endoscopic diagnosis of esophageal columnar metaplasia from one that is confirmed histologically. Recent studies have shown that there may be a marked disparity between endoscopic and biopsy findings. In one recent study, a group of patients with suspected Barrett's esophagus at endoscopy and no evidence of intestinal metaplasia at biopsy underwent repeat endoscopy 2 yr later (123). At the second examination, 42% of patients had no endoscopic or histological evidence of Barrett's esophagus and 46% continued to have apparent Barrett's esophagus at endoscopy without biopsy confirmation of intestinal metaplasia. These data suggest that the endoscopic diagnosis needs confirmation with histology and that a term that acknowledges the possibility that the endoscopic appearance may not be diagnostic was chosen. The option "endoscopically suspected Barrett's esophagus" was considered, but the more neutral, descriptive terminology given in the statement was preferred, in the belief that this would be of less concern to patients and their insurers and would prevent patients from being mistakenly labeled as having Barrett's esophagus before histological confirmation was obtained (131) (Fig. 3).

**36. Multiple, closely spaced biopsies are necessary to characterize ESEM**

Level of agreement: A+, 79%; A, 17%; A-, 0%; D-, 2%; D, 2%; D+, 0% (*Grade: High*)

Effective management of the risk for esophageal adenocarcinoma requires sensitive detection of intestinal-type metaplasia (see Statement 41) and high-grade dysplasia (122,

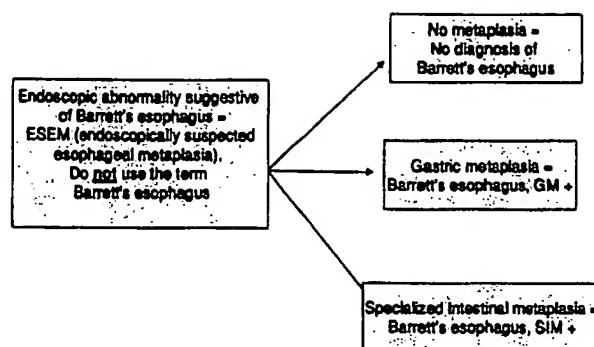


Figure 3. Consensus terminology for Barrett's esophagus.

132). These histological abnormalities, particularly high-grade dysplasia, frequently occupy a very small proportion of the surface area of columnar metaplasia (133, 134). Though research into novel endoscopic techniques suggests that it may, in the future, be possible to recognize areas of metaplastic mucosa likely to contain changes of particular clinical relevance and to target biopsies to these areas, this is currently not an established option in routine clinical practice (135, 136). Thus, current biopsy practice must sample all areas of metaplastic mucosa as thoroughly as possible (122, 132). The best researched biopsy protocol is four-quadrant biopsies every 1 cm for circumferential metaplastic segments, which is substantially more sensitive than sampling at 2-cm intervals (133, 137). This approach has been variably modified to include biopsies at the top of tongue-like metaplastic extensions. These onerous and usually expensive protocols are generally not accepted as best practice (122, 132). Even with the use of such protocols, there is still evidence of significant sampling inaccuracies, since concordance for the finding of presence or absence of intestinal-type metaplasia between first, second, and even third endoscopies is relatively poor, especially for segments shorter than 3 cm (123, 138, 139). It has been found that intestinal-type metaplasia is most prevalent at the most proximal extent of metaplasia (140).

**37. The description of ESEM should include a standardized measure of endoscopic extent**

Level of agreement: A+, 88%; A, 12%; A-, 0%; D-, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

Reliable unambiguous measures of extent are desirable for clinical communication and research into esophageal columnar metaplasia. The risk for adenocarcinoma is significantly influenced by the extent of metaplasia. If all esophageal columnar metaplasia is considered, around three quarters of cases appear to have metaplasia less than 3 cm in extent and the cancer risk is less in these patients than in those with more extensive metaplasia (98, 141, 142). There is an evidence of a continuum of increasing risk for cancer with increasing extent of metaplasia beyond 3 cm (98, 143).

"Standardized" is an important qualifying word in the statement. There has been insufficient research into the best approaches to endoscopic measurement of extent.

Accordingly, differing approaches have been used in published studies, with resultant difficulties in making comparisons among studies or with pooling their data. The lack of a validated, standard approach to measurement of extent means that this clinically relevant variable is often poorly described and in terms that are open to interpretation. Recently, however, an international working group has developed standard criteria that may aid further research (144).

**38. When biopsies of ESEM show columnar epithelium it should be called Barrett's esophagus and the presence or absence of intestinal-type metaplasia specified**

Level of agreement: A+, 49%; A, 28%; A-, 9%; D-, 5%; D, 2%; D+, 7% (*Grade: Not applicable*)

This statement is the final product of the most controversial topic of the workshop. In the early phase of discussion it was decided that the eponymous term "Barrett" should be retained in any definition because it would be futile and counterproductive to try to remove such an embedded word from general use. Pragmatism aside, opinion was divided as to whether Barrett's original scientific contribution warranted continued use of his name as a label, but this was not put to formal discussion and voting. With retention of the word "Barrett" decided, there was eventual consensus that all types of histologically proven esophageal columnar metaplasia should be included under this umbrella word, with the important added descriptors of either "intestinal-type metaplasia positive" or "negative" (see statement above). One major reason for the statement and the voting on it was the far from perfect sensitivity of even a rigorous biopsy protocol for detection of intestinal-type metaplasia (see Statement 36), let alone the less rigorous biopsy protocols used in routine clinical practice in every part of the world where practice has been surveyed (145-147). This is not just a problem of tissue sampling, since the staining techniques and interpretation of biopsies can influence the sensitivity of detection of intestinal-type metaplasia (148, 149). A literature search failed to reveal any systematic review or meta-analysis of the risk for esophageal adenocarcinoma of definite esophageal columnar metaplasia in which intestinal metaplasia had not been shown to be present, despite careful biopsy sampling (Fig. 3).

*Adenocarcinoma:*

**39. Adenocarcinoma of the esophagus is a complication of GERD**

Level of agreement: A+, 67%; A, 26%; A-, 7%; D-, 0%; D, 0%; D+, 0% (*Grade: Moderate*)

**40. The risk of adenocarcinoma of the esophagus rises with increasing frequency and duration of heartburn**

Level of agreement: A+, 47%; A, 42%; A-, 7%; D-, 0%; D, 2%; D+, 2% (*Grade: Moderate*)

There is strong epidemiological evidence, especially from case-control studies in Sweden, that esophageal adenocarcinoma is a complication of GERD and that chronic GERD symptoms increase the risk of esophageal adenocarcinoma

(97, 98). In the study by Lagergren *et al.* the risk of esophageal adenocarcinoma was increased (OR 7.7) in patients suffering from longstanding reflux symptoms (97). Higher frequency (greater than 3 times per week) and long duration (greater than 10-20 yr) of symptoms further increased the OR to 16.4 and 20. Over the last 25 yr there has been a remarkable change in the epidemiology of esophageal cancer in Western countries. The incidence of esophageal adenocarcinoma has been rising substantially although the absolute lifetime risk of developing adenocarcinoma is <1% (97, 150-152). In addition, until recently, the incidence of esophageal squamous cell carcinoma used to be much higher than esophageal adenocarcinoma. According to recent data from the United States, the incidence of adenocarcinoma of the esophagus now has surpassed the rate of squamous carcinoma (151). The rise in adenocarcinoma incidence is in keeping with the rising GERD prevalence in other parts of the world. For example in Japan, where the disease used to be rare, the prevalence of GERD is increasing, as are Barrett's esophagus and esophageal adenocarcinoma (153, 154).

**41. Long-segment Barrett's esophagus with intestinal-type metaplasia is the most important identified risk factor for esophageal adenocarcinoma**

Level of agreement: A+, 67%; A, 21%; A-, 12%; D-, 0%; D, 0%; D+, 0% (*Grade: High*)

A wealth of consistently supportive data resulted in prompt consensus on this statement (see Statement 37) (97, 132, 155, 156). Wang *et al.* have tabulated the reported experience on adenocarcinoma development from endoscopic surveillance studies (132). A large scale prospective Swedish study of patients with the diagnosis of esophageal adenocarcinoma provides the most definitive data (97). It is unclear what proportion of the esophageal columnar metaplasia-negative cases noted in this study were accounted for either by destruction of esophageal columnar metaplasia by cancer or by misclassification of adenocarcinoma of the gastric cardia as esophageal adenocarcinoma (97).

**EXTRAESOPHAGEAL SYNDROMES: ESTABLISHED ASSOCIATIONS.** Although a great amount has been published on the extraesophageal GERD syndromes, little of this represents high-level original work. This realization prompted an evolution in the statements regarding the extraesophageal syndromes, as paucity of evidence supporting the initial versions became apparent. Thus, whereas in the initial iterations, the statements strongly suggested causality between reflux and cough, laryngitis, asthma, and dental erosions, the final iterations were much more restrained, emphasizing (1) the existence of an association between these syndromes and GERD, (2) the rarity of extraesophageal syndromes occurring in isolation without a concomitant manifestations of the typical esophageal syndrome, (3) that these syndromes are usually multifactorial with GERD as one of the several potential aggravating cofactors, and (4) that data



substantiating a beneficial effect of reflux treatments on the extraesophageal syndromes are weak.

*Reflux cough, reflux laryngitis, and reflux asthma syndromes:*

**42. Chronic cough, chronic laryngitis, and asthma are significantly associated with GERD**

Level of agreement: A+, 39%; A, 26%; A-, 28%; D-, 7%; D, 0%; D+, 0% (*Grade: High*)

**43. Chronic cough, chronic laryngitis, and asthma are usually multifactorial disease processes and gastroesophageal reflux can be an aggravating cofactor**

Level of agreement: A+, 63%; A, 23%; A-, 12%; D-, 2%; D, 0%; D+, 0% (*Grade: Cough Low, Laryngitis Low, Asthma High*)

**44. Gastroesophageal reflux is rarely the sole cause of chronic cough, chronic laryngitis, or asthma**

Level of agreement: A+, 65%; A, 23%; A-, 7%; D-, 5%; D, 0%; D+, 0% (*Grade: Cough Low, Laryngitis Very Low, Asthma High*)

Three large population-based surveys have demonstrated an increased risk of numerous ENT and pulmonary symptoms among patients with either esophagitis or reflux symptoms (81, 157, 158). The reported ORs for having laryngeal or pulmonary conditions among GERD patients in these studies range from 1.2 to 3.0, with nocturnal cough having the strongest association.

Support for the premise that chronic cough, chronic laryngitis, or asthma are multifactorial processes with reflux as a potential aggravating factor comes from therapeutic trials in which these entities were improved, but incompletely resolved, by treating reflux disease. In the case of reflux cough syndrome, the only randomized controlled trials of medical therapy found no treatment effect (159–161). Thus, one has to look to observational trials of antireflux surgery (162–164) and these are by nature subject to selection and referral bias. By and large these trials show improvement in cough scores as a result of treatment. With respect to reflux laryngitis syndrome, there are no randomized controlled treatment trials in which chronic laryngitis patients exhibited a complete treatment response. Observational trials of medical or surgical therapy report partial improvement in laryngitis symptomatology and in some cases laryngoscopic appearance (164, 165). Commonly implicated cofactors with laryngitis include heavy voice usage, habitual throat clearing, allergic rhinitis with postnasal drip, infectious laryngitis, and environmental irritants including smoking. Regarding reflux asthma syndrome, Field summarized the medical and surgical data and concluded that there was a significant benefit in improving asthma symptoms and reducing asthma medication usage but no improvement in pulmonary function attributable to GERD therapy (166, 167). Commonly implicated cofactors among asthma patients include allergens, exercise, temperature or climate changes, or emotional conflicts.

Since reflux disease has highly effective treatments, it follows that manifestations of the disease should exhibit high-grade treatment effects. Thus, support for the premise that reflux is the sole cause of chronic cough, chronic laryngitis, or asthma would come from therapeutic trials in which these entities were completely resolved by treating reflux disease. In the case of chronic cough, few, if any, patients within randomized controlled trials exhibited a complete treatment response (159–161). The strongest evidence of a complete treatment effect comes from an uncontrolled observational study of laparoscopic Nissen fundoplication in which 51% of 133 chronic cough patients exhibited a complete symptom response following the procedure (162). In a smaller observational study of 8 carefully studied chronic patients who were refractory to medical therapy, 2 subsequently exhibited a complete cough resolution after antireflux surgery (163). Both of these series enrolled highly selected patients, suggesting that although chronic cough can be entirely attributable to reflux, this is a rare occurrence. With respect to chronic laryngitis, there are no randomized controlled treatment trials for GERD in which patients exhibited a complete treatment response. Observational treatment trials of medical or surgical therapy report partial symptomatic improvement and in some cases laryngoscopic appearance but few, if any, patients experienced a complete laryngitis response (164, 165). With respect to reflux asthma syndrome, Field concluded that there was no objective improvement in pulmonary function attributable to medical therapy of GERD (166). Furthermore, a recent longitudinal epidemiological study of more than 14,000 patients in U.K. general practice found that patients with a new diagnosis of asthma are at significantly increased risk for developing GERD rather than *vice versa* (168). However, two randomized controlled trials of antireflux surgery as treatment for asthma reported subsets of patients in the surgically treated arms with complete asthma resolution; 6 of 16 in the Sontag *et al.* study and 11 of 22 in the Larrain *et al.* study (169, 170). Pulmonary function data are not provided in the Larrain *et al.* study. Thus, only a subset of patients has asthma entirely attributable to reflux, and this subset is probably small.

**45. Potential causal mechanisms of reflux cough, reflux laryngitis, and reflux asthma syndromes include direct (aspiration) or indirect (neurally mediated) effects of gastroesophageal reflux**

Level of agreement: A+, 61%; A, 28%; A-, 7%; D-, 2%; D, 0%; D+, 2% (*Grade: High*)

Experimental evidence in both animals and humans has demonstrated reflex stimulation of bronchospasm and cough as a response to esophageal acidification (171, 172). Animal studies have also demonstrated the development of laryngeal ulceration and profound bronchospasm as a result of the direct application of acid to the larynx or acid instillation into the airway (173, 174). Studies of pulmonary function in asthmatics have demonstrated correlation between lung



resistance and the occurrence of spontaneous gastroesophageal reflux (175).

**46. In the absence of heartburn or regurgitation, unexplained asthma and laryngitis are unlikely to be related to GERD**

Level of agreement: A+, 37%; A, 33%; A-, 14%; D-, 7%; D, 9%; D+, 0% (*Grade: Laryngitis Low, Asthma High*)

This statement implies that individuals with conclusive reflux laryngitis and reflux asthma syndromes usually have esophageal manifestations of reflux as well. Since the only patients in whom these diagnoses can be confidently established are those that convincingly responded to reflux treatment, it is the responders who must be evaluated with respect to whether or not they had frequent heartburn. With respect to reflux laryngitis syndrome, the only randomized controlled trials demonstrating a treatment effect were on patients with clear-cut reflux disease in addition to the laryngitis, whereas the recent trial that excluded patients with frequent heartburn demonstrated no benefit of a PPI over placebo in treating the laryngitis (176–178). With respect to asthma, most asthmatics have objective evidence of reflux disease as well as reflux symptoms (179). A recent randomized controlled study of 770 asthmatics evaluated twice-daily PPI therapy and only the patient group with both nocturnal respiratory and GERD symptoms responded to the PPI better than to placebo in the primary study outcome measure (morning peak expiratory flow) (180). In the two randomized controlled trials of antireflux surgery that showed treatment benefit with respect to asthma, objective evidence of reflux was either an entry criterion for the study or objectively demonstrated in almost all patients (169, 170).

**47. Medical and surgical treatment trials aimed at improving presumed reflux cough, reflux laryngitis, and reflux asthma syndromes by treating GERD are associated with uncertain and inconsistent treatment effect**

Level of agreement: A+, 51%; A, 40%; A-, 7%; D-, 0%; D, 0%; D+, 2% (*Grade: Cough Very Low, Laryngitis Moderate, Asthma High*)

In the case of reflux cough syndrome, two small randomized controlled trials have evaluated the effects of PPI treatment on chronic cough. One of these found no significant improvement in cough between the PPI and placebo groups (12% vs 0%) with only 1 of 8 patients randomized to the PPI showing a response (159). However, during subsequent, open-label treatment 5 of the 9 placebo-treated patients, all of whom had markedly abnormal pH studies, responded dramatically. The other randomized controlled PPI trial was compromised by a crossover design that the authors concluded resulted in treatment effect from the first period carrying over to the second. When the analysis was restricted to the group randomized to initial placebo therapy (N = 13), a significant reduction in cough score was demonstrated when they crossed over to PPI (160). Crossover studies are prone

to overestimating treatment effect and these studies should be viewed with caution. One randomized controlled trial of H<sub>2</sub>-receptor antagonist therapy for chronic cough showed no therapeutic benefit (161). Several uncontrolled trials on H<sub>2</sub>-receptor antagonists, with or without prokinetics, have reported improvement in cough in 70–100% of treated patients (176, 177, 181, 182). With respect to treatment of suspected reflux cough syndrome with antireflux surgery, there are no controlled trials. There are, however, consistently positive results from uncontrolled studies suggesting benefit in a subset of chronic cough patients but these studies have the usual limitations in that they overestimate treatment effect (164, 183).

For reflux laryngitis there are four published randomized controlled trials using twice-daily PPI therapy for 8–12 wk encompassing a total of 88 patients (176, 177, 181, 182). One additional study of 88 patients has thus far been published only in abstract form (178). One trial showed a significant difference between the PPI and placebo in resolution of laryngeal symptoms and one other for hoarseness and throat clearing (159, 177). No significant difference in laryngoscopic healing was found between placebo and PPI-treated groups in any of the trials. There are substantial inconsistencies among the trials in laryngoscopic criteria for defining reflux laryngitis, pH-monitoring protocols, and most importantly, inclusion of patients with concomitant heartburn. The trial with the best therapeutic result enrolled patients with high-grade, unequivocal laryngoscopic findings and markedly abnormal esophageal pH-monitoring studies (161). The large treatment trial finding no PPI benefit enrolled patients with low-grade laryngoscopic findings and excluded patients with frequent heartburn (178).

With respect to reflux asthma syndrome, Field concluded that there was a significant benefit in improving asthma symptoms and reducing asthma medication usage but no objective improvement in pulmonary function attributable to GERD therapy (166, 170, 184–190). A recent large study, using esomeprazole 40 mg twice daily, enrolled a total of 770 patients and subdivided asthmatics into those with only nocturnal respiratory symptoms, only nocturnal GERD symptoms, or both nocturnal respiratory and GERD symptoms. The primary outcome variable was the change in morning peak expiratory flow. Of the three patient groups, only those with both nocturnal respiratory and GERD symptoms responded to esomeprazole better than to placebo with a mean difference in morning peak expiratory flow of 8.7 L/min (180). A difference of 20 L/min is generally considered the threshold for clinical significance. Also of interest is a recent study analyzing a subset of asthmatic patients with cough and reflux (191). This uncontrolled treatment trial demonstrated substantial improvement in cough, pulmonary function, asthma symptoms, and reflux symptoms (when present) after 3 months of PPI therapy (esomeprazole 40 mg once daily). In a complementary analysis of the effects of antireflux surgery on asthma, there were only two controlled trials again showing improvement

in asthma symptoms and medication use but no improvement in pulmonary function (167, 169, 170). Similar to the case with the laryngitis studies, there are substantial inconsistencies among trials in asthma definition and in whether or not patients with well-defined or symptomatically evident GERD were included. Of particular note, the largest placebo-controlled trial of surgical therapy was a three-armed trial involving 90 patients conducted by a single group of investigators (170). This trial, which reported the best therapeutic results in both the medical and surgical domain, excluded patients with "allergic" asthma and required that they had reflux symptoms.

#### *Reflux dental erosion syndrome:*

48. The prevalence of dental erosions, especially on the lingual and palatal tooth surfaces, is increased in patients with GERD

Level of agreement: A+, 42%; A, 35%; A-, 19%; D-, 2%; D, 0%; D+, 2% (Grade: High)

In a prospective consecutive series, 253 patients were divided into two groups based on reflux symptoms: 181 refluxers and 72 controls (192). The percentage with dental erosions was significantly higher among the reflux group (47.5% vs 12.5%  $p < 0.001$ ) but there were no differences in other clinical or dental parameters. A similar analysis among intellectually disabled individuals found 19 of 29 individuals (65.5%) with dental erosions to have pH-monitoring criteria for GERD compared to only 9 of 34 without dental erosions (26.5%) ( $p = 0.04$ ) (193). Another study found a positive correlation between esophageal acid exposure measured by pH monitoring and dental erosion score among 30 patients with and without GERD (194).

#### EXTRAESOPHAGEAL SYNDROMES: PROPOSED ASSOCIATIONS.

49. It is unclear whether gastroesophageal reflux is a significant causal or exacerbating factor in the pathogenesis of sinusitis, pulmonary fibrosis, pharyngitis, or recurrent otitis media

Level of agreement: A+, 91%; A, 9%; A-, 0%; D-, 0%; D, 0%; D+, 0% (Grade: Low, reflecting lack of authoritative mechanistic or therapeutic studies)

The generally low quality, uncontrolled published studies relevant to this statement have been reviewed recently (195, 196). Epidemiological studies have shown a modestly increased OR for sinusitis in the U.S. military veterans with reflux esophagitis of 1.6 (1.51–1.70) (157). This risk is slightly higher at 2.34 (1.72–3.19) for children with GERD (197). Adequate evidence of causal linkage is lacking. U.S. military veterans with reflux esophagitis have a slightly increased risk for idiopathic pulmonary fibrosis, with an OR of 1.36 (1.25–1.48) (157). There is no persuasive evidence of causal linkage. There are no authoritative, confirmed data that indicate

GERD is a clinically significant contributor to pharyngitis or otitis media.

50. It is unclear whether gastroesophageal reflux plays a role in triggering apneic episodes in patients with obstructive sleep apnea

Level of agreement: A+, 74%; A, 21%; A-, 5%; D-, 0%; D, 0%; D+, 0% (Grade: Low, because of lack of direct mechanistic study data)

An increased prevalence of GERD has been found consistently in obstructive sleep apnea patients, but uncertainty remains whether reflux episodes are true precipitants of apneic episodes (198–204). The argument that lack of correlation of severity of reflux-induced symptoms with severity of obstructive sleep apnea is an evidence against precipitation of apneic episodes by reflux episodes is unconvincing (205). More definitive mechanistic data are required.

#### CONCLUSIONS

In conclusion, a new definition and classification of GERD has been developed by an International Consensus Group. It provides a basis for universally accepted terminology that bridges cultures and countries and may simplify disease management, allow collaborative research, and make studies more generalizable, assisting patients, physicians, and regulatory agencies. Coupling evidence-based medicine with modern consensus development techniques allows a broad consensus among different regions of the world. For practicing physicians, this definition and classification clarify the criteria necessary for a diagnosis of GERD, simplify the classification of suspected and proven Barrett's esophagus, and define the state of our incomplete knowledge in extraesophageal disorders. For patients, the consensus statement provides clarity on a diagnosis that is based on a patient-centered definition of troublesome symptoms and may help to prevent patients from being inappropriately labeled as having Barrett's esophagus. Clarification of the role of GERD in patients with cough and hoarseness may also help the management of patients with these difficult conditions. Finally, regulators may benefit from a uniform terminology and classification to use with clinical trial data submissions.

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Reprint requests and correspondence: Nimish Vakil M.D., F.A.C.G., ASMC, 945 North 12th Street, Room 4040, Milwaukee, WI 53233.

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Guarantor of the article: Nimish Vakil

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Esophageal Syndromes, Symptomatic: Roger Jones

Syndromes with esophageal injury (reflux esophagitis and stricture): Sender van Zanten

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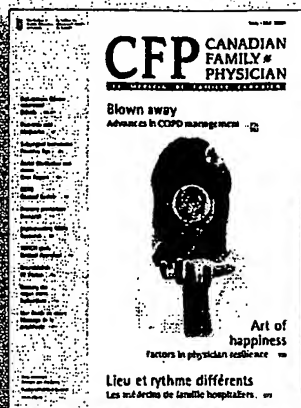
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Those who desire air and quick recovery should go to the hills, where the wind has the scent of sunbeams.

John Richard Jeffries  
The Life of the Fields, 1884

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# MFC MÉDECIN DE FAMILLE CANADIEN

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## Approach to gastroesophageal reflux disease in primary care

### *Putting the Montreal definition into practice*

Nigel Flook MD Roger Jones DM Nimish Vakil MD

#### ABSTRACT

**OBJECTIVE** To apply the recently published Montreal definition of gastroesophageal reflux disease (GERD) in primary care.

**SOURCES OF INFORMATION** The Montreal definition of GERD was developed by an international consensus group of experts in GERD and primary care physicians using rigorous evidence-based methods along with modern consensus development techniques and a patient-centred approach.

**MAIN MESSAGE** Gastroesophageal reflux disease can be diagnosed in primary care based on symptoms alone without additional diagnostic testing. Symptoms reach a threshold where they constitute disease when they are troublesome (cause difficulty) to patients. In addition to the cardinal symptoms of heartburn and regurgitation, people with GERD can also have sleep disturbances, chest pains, or respiratory symptoms. Monitoring patients' response to proton pump inhibitor therapy can confirm the success of management. Treatment for symptoms of GERD can also heal underlying reflux esophagitis if it is present.

**CONCLUSION** Primary care physicians can diagnose and manage GERD confidently in most patients by investigating and treating troublesome symptoms without the need for additional investigations or referral to specialists.

#### RÉSUMÉ

**OBJECTIF** Mettre en pratique dans les soins primaires la définition de Montréal du reflux gastro-œsophagien (RGO) récemment publiée.

**SOURCES DE L'INFORMATION** La définition de Montréal du RGO a été développée par un groupe de spécialistes du RGO et de médecins de première ligne internationaux réunis pour faire des recommandations, grâce à des méthodes fondées sur des preuves rigoureuses et à des techniques modernes de développement de consensus, et en adoptant une approche centrée sur le patient.

**PRINCIPAL MESSAGE** On peut diagnostiquer le reflux gastro-œsophagien en médecine primaire à partir des seuls symptômes, sans test diagnostique additionnel. C'est lorsque les symptômes deviennent gênants pour la patient qu'on peut parler de maladie. Outre les symptômes cardinaux de pyrosis et de régurgitation, on peut aussi observer des troubles du sommeil, douleurs thoraciques ou symptômes respiratoires. L'observation de la réponse aux inhibiteurs de la pompe à protons peut confirmer le succès du traitement. Le traitement des symptômes du RGO peut aussi guérir une œsophagite de reflux sous-jacente.

**CONCLUSION** Le médecin de première ligne peut diagnostiquer et traiter sans crainte la plupart des cas de RGO en investiguant et en traitant les symptômes incommodes sans recourir à des examens additionnels ou à des spécialistes.

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**T**he first ever global consensus definition of gastroesophageal reflux disease (GERD), the Montreal definition, was published recently.<sup>1</sup> Developed by an international consensus group of experts and family physicians, the Montreal definition was built using rigorous evidence-based methods along with modern consensus development techniques. The Montreal definition describes a symptom-based, patient-centred approach to diagnosis of GERD. This approach includes a measure of the severity of symptoms by stating that GERD is "a condition that develops when the reflux of gastric content causes troublesome symptoms or complications."<sup>1</sup>

Heartburn and regurgitation are the characteristic symptoms of GERD. Heartburn is defined as a burning sensation in the retrosternal area. Regurgitation is defined as the perception of flow of refluxed gastric contents into the mouth or hypopharynx. These symptoms are sufficiently descriptive to be diagnostic. Esophageal and extraesophageal symptoms and syndromes that form part of the framework of GERD also include chest pain, sleep disturbances, cough, hoarseness, and asthma (Figure 1).<sup>1</sup> This article aims to encourage physicians to use the Montreal definition to diagnose and manage GERD in primary care. We present an illustrative case description.

### Case description

George is a 48-year-old computer programmer who enjoys playing squash in a top-tier league 3 times a week. He consults his primary care physician because for a year he has had a persistent cough that wakes him in the night several times a week. The cough is accompanied by regurgitation and is often associated with nonradiating retrosternal pain. George occasionally sips water to try to "settle the cough," but this gives little relief. The sleep disturbances associated with these symptoms lead to tiredness and difficulty concentrating at work. George also gets retrosternal pain and regurgitation during the day, particularly after a large meal. He worries that the chest discomfort could be a sign of heart disease because of his stress at work, and he hopes treatment will restore his productivity at work.

### Sources of information

The Montreal definition and classification of GERD was developed by an international consensus group of

experts and family physicians over a period of 2 years.<sup>1</sup> A series of statements was drafted based on evidence from systematic reviews of the literature in 3 databases (EMBASE, Cochrane Central Register of Controlled Trials, and MEDLINE). The group went through 4 rounds of voting to modify and approve the statements.

### Diagnosis

#### *Symptom-based diagnosis of GERD (level III evidence).*

The primary care physicians who contributed to the Montreal definition were convinced of the importance of a symptom-based, patient-centred approach to care of people with GERD. This approach was overwhelmingly accepted by the international experts.

The Montreal definition recognizes that GERD can be diagnosed in primary care on the basis of symptoms alone without additional diagnostic testing.<sup>1,2</sup> This approach is appropriate for most patients and does not use unnecessary resources. Symptoms reach a threshold where they constitute disease when they are troublesome to patients and affect their functioning during usual activities of living. This patient-centred approach to diagnosis includes asking patients how their symptoms affect their everyday lives.

*Chest pain (level II evidence).* Symptoms of GERD can be experienced in the chest or upper abdomen and might be described as burning or painful. Chest pain induced by GERD can closely mimic ischemic heart pain.<sup>1,3,4</sup> In managing such cases, a prudent first step is to exclude heart disease as the cause of the pain.

Gastroesophageal reflux disease is thought to cause the chest pain of nearly half the patients with noncardiac chest pain. Patients are often left untreated once cardiac causes have been excluded; studies show that these people then use more health care resources than they did before and suffer functional impairment that goes unresolved until they are correctly diagnosed and treated.<sup>5,6</sup>

*Serious sleep disturbances (level II evidence).* Patients with GERD frequently wake up at night or are unable to get to sleep because of their symptoms.<sup>7</sup> Symptoms can be worse when patients lie down. In fact, GERD is a main cause of unexplained sleep disturbances. Sleep disturbances, as well as nighttime reflux symptoms, improve substantially with proton pump inhibitor (PPI) therapy.<sup>8</sup>

### Levels of evidence

**Level I:** At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

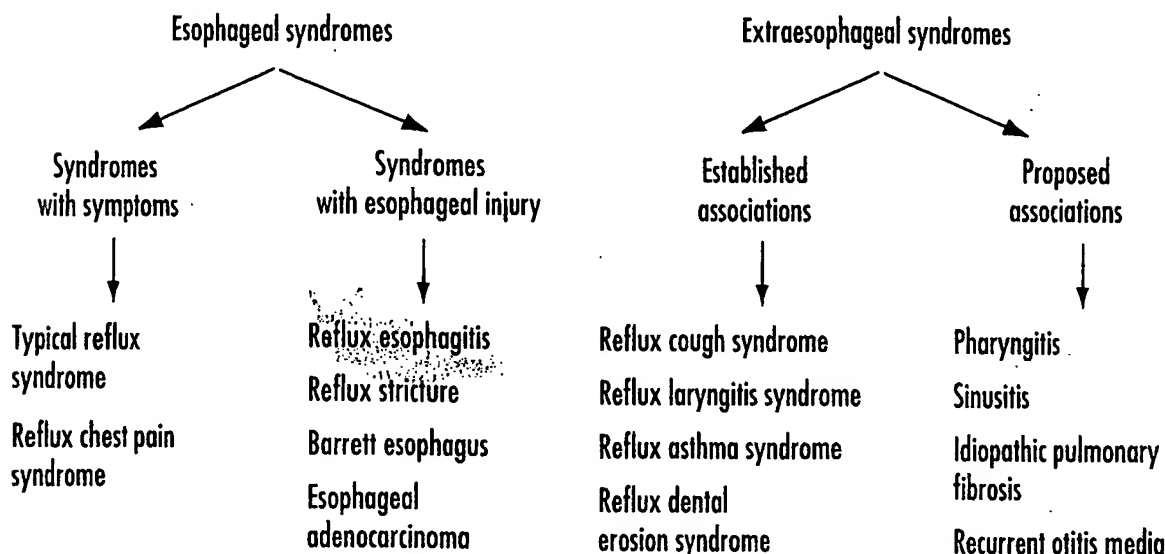
**Level II:** Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

**Level III:** Expert opinion or consensus statements

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*Dr Flook is a family physician and an Associate Clinical Professor in the Department of Family Medicine at the University of Alberta in Edmonton. Dr Jones teaches at King's College in London, England. Dr Vakil is a Clinical Professor of Medicine at the University of Wisconsin School of Medicine and Public Health in Madison and also teaches at the Marquette University College of Health Sciences in Milwaukee.*

**Figure 1.** The Montreal definition of gastroesophageal reflux disease and its constituent syndromes: *Gastroesophageal reflux disease is a condition that develops when the reflux of gastric content causes troublesome symptoms or complications.*



Reprinted with permission from Vakil et al.<sup>1</sup>

Uncertainty remains as to whether reflux plays a role in triggering apneic episodes in patients with obstructive sleep apnea.<sup>1,9</sup> Obesity is a contributory factor to both GERD and obstructive sleep apnea, but the 2 diseases might not be causally related.

**Respiratory problems (level II evidence).** The respiratory syndromes associated with GERD include cough, asthma, and laryngitis.<sup>1,10-12</sup> These respiratory symptoms are typically accompanied by the cardinal symptoms of heartburn or regurgitation. There are occasional exceptions to this, particularly among elderly people.<sup>12</sup> Respiratory problems can be aggravated by GERD, which usually acts as a cofactor in the multifactorial etiology of respiratory conditions, such as asthma or chronic obstructive pulmonary disease. When patients do not have heartburn and regurgitation, GERD is unlikely to be a substantial cofactor in respiratory conditions.

Searching for symptoms of GERD will often be helpful to patients whose respiratory symptoms are poorly controlled despite usual management. Gastroesophageal reflux disease might lead to extraesophageal symptoms if patients aspirate refluxed gastric contents or might stimulate the vagus nerve and bring on reflex bronchoconstriction.<sup>13,14</sup>

### Management: the next step

**Endoscopy is a poor guide to management (level II evidence).** When large groups of patients are evaluated, a correlation can be seen between the severity of

symptoms and the severity of underlying esophageal damage caused by GERD, such as reflux esophagitis. Unfortunately, for individual patients with GERD, the correlation between severity of symptoms and endoscopic findings is poor.<sup>1,15</sup> Also, most patients with GERD have no visible evidence of esophagitis at endoscopy, making endoscopic appearance a poor guide to diagnosis and management of GERD. Negative endoscopic findings in the presence of troublesome heartburn or regurgitation are entirely consistent with GERD.<sup>1</sup> Patients in these cases are said to have nonerosive reflux disease. Other tests to diagnose GERD, such as esophageal pH monitoring, will not outperform symptom-based diagnosis. Esophageal pH monitoring is not highly sensitive; results of a second test are positive in about one-quarter to one-third of patients whose first test results were negative.<sup>16,17</sup> The implication for primary care physicians is that only a few patients need referral for endoscopy or other diagnostic testing for GERD. The few requiring referral include those with long-standing (longer than 5 years) symptoms or symptoms that are unresolved by PPI therapy and those with alarm features. Alarm features include vomiting, gastrointestinal bleeding or anemia, abdominal masses or unexplained weight loss, and progressive dysphagia.<sup>2</sup>

**Acid suppression therapy can guide management (level III evidence).** Regurgitation of gastric acid into the lower esophagus is by far the most common cause of GERD. This is why PPI therapy is effective.<sup>1,18</sup> Monitoring



patients' response to PPI therapy is an ideal way to assess the success of management. A few patients will be unresponsive to PPI therapy because they have symptoms caused by reflux of bile containing duodenal contents through the stomach and into the esophagus.<sup>1</sup>

**Serious complications (level II evidence).** The spectrum of reflux disease runs from nonerosive reflux disease through to esophageal complications, such as esophagitis, hemorrhage, and stricture, and to Barrett esophagus and esophageal adenocarcinoma.<sup>1</sup> These complications are thought to be due to prolonged and repeated esophageal exposure to acid. Treatment for symptoms of GERD can also heal esophagitis.<sup>19</sup> When the diagnosis has been made based on symptoms and a PPI has been chosen for treatment, clinicians can be confident that such treatment is the most effective choice for both the symptoms and the underlying esophagitis, if it is present. Symptom resolution with PPI therapy provides added reassurance about the initial symptom-based diagnosis.

**Dysphagia is progressive in a few GERD patients (level II evidence).** Symptoms of GERD can at times lead to some difficulty swallowing food and liquids, and this can cause patients to worry about progressive disease, such as esophageal cancer. Nonprogressive dysphagia is common in patients with GERD, however, and resolves in most patients following treatment with a PPI.<sup>20</sup> Dysphagia that gets progressively worse, especially regarding solids, is far less common and represents an alarm feature that warrants further investigation to search for esophageal malignancy or peptic stricture.<sup>21</sup> A careful history can identify patients with worrisome symptoms of dysphagia. Referral for contrast studies and endoscopy should not be a reflex response because treatment with a PPI will resolve the nonprogressive dysphagia commonly associated with GERD in most patients.

**Barrett esophagus can be diagnosed only on the basis of esophageal histology (level III evidence).** Barrett esophagus is an important marker for changes in the lower esophagus that are associated with increased risk of adenocarcinoma of the esophagus. The proportion of GERD patients in primary care who have Barrett esophagus is unknown but is estimated to be only a few of those with long-standing GERD. The Montreal definition of GERD provides a revised global consensus definition of Barrett esophagus. Endoscopically suspected *endothelial metaplasia* is the new agreed-upon term for endoscopic findings consistent with Barrett esophagus.<sup>1</sup>

When biopsies of endothelial metaplasia show columnar epithelium, the condition should be called *Barrett esophagus* and the presence or absence of intestinal-type metaplasia specified.<sup>1</sup> The revised terminology will help primary care physicians to understand the

endoscopic and histologic reports they receive and the rationale for including some patients in cancer surveillance programs. Patients with long-standing (more than 5 years) and frequent symptoms, particularly obese men older than 50 years, should be considered for endoscopy to search for Barrett esophagus.<sup>1,2</sup>

**Treatment recommendations (level I evidence).** Important treatment choices for GERD include PPIs and histamine H<sub>2</sub> receptor antagonists. There is strong evidence in the literature to support using PPIs because they have superior efficacy compared with histamine H<sub>2</sub> receptor antagonists, and this effectiveness comes with equivalent safety. Cost and availability of treatment options are important considerations and will require difficult decisions to be made based on individual and local factors. The emphasis on treatment with PPIs is consistent with recommendations from the current Canadian Consensus Guidelines on Treatment of GERD. This article reports the results of a comprehensive review of the literature and makes recommendations based on a Delphi consensus process. Clinicians reviewing this article will find clear and concise statements to guide their therapeutic choices when treating patients with GERD.<sup>22</sup>

### Case resolution

George's family doctor reassured him that his chest pain was very unlikely to have a cardiac cause because he was able to play squash at a high level 3 times a week without any chest discomfort. He was diagnosed with GERD based on his symptoms. He has been taking a PPI for 1 month, and his symptoms have improved substantially. He is sleeping well because his cough no longer wakes him. George now feels reassured that his chest pain is not a sign of coronary artery disease, especially as he has not experienced any further chest pain since completing a month of treatment with a PPI. He notices his concentration and work productivity have improved since he has been sleeping better and feeling more rested. He no longer worries about his symptoms, and his quality of life has returned to normal.

### Conclusion

The Montreal definition provides a patient-centred, symptom-based approach to diagnosis and management of GERD that will fit well with the care plans of most family physicians. Most patients can be confidently diagnosed based on troublesome symptoms that can be attributed to GERD. Primary care physicians can diagnose and manage most GERD patients without the need for additional investigations or referral to specialists. The Montreal definition can assist primary care physicians in providing safe and effective care for most patients who have GERD. ✱



### Competing interests

Dr Flook has been involved in continuing medical education or consensus development, received speaker fees or research grants, or been an advisory board member for Altana, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Ortho, Merck, Pfizer, and Wyeth. Dr Jones has received consultancy and speaking fees from AstraZeneca and Pfizer that involved giving presentations on various aspects of upper gastrointestinal disorders, providing advice on trial design, and taking part in the development of the Montreal definition of gastroesophageal reflux disease.

**Correspondence to:** Dr N. Flook, University of Alberta Hospital, 1A1.11, 8440-112 St, Edmonton, AB T6G 2B7; telephone 780 433-4211; fax 780 407-1828; e-mail nflook@shaw.ca

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### EDITOR'S KEY POINTS

- Gastroesophageal reflux disease (GERD) can be diagnosed based on symptoms alone without additional diagnostic testing. The Montreal definition of GERD describes a symptom-based, patient-centred approach to diagnosis of GERD.
- Response to acid suppression therapy—proton pump inhibitors and histamine H<sub>2</sub> receptor antagonists—can guide management. In individual patients, the correlation between endoscopy findings and symptom severity is poor.
- Endoscopy should be considered in those with long-standing (more than 5 years) and frequent GERD symptoms to search for Barrett esophagus, as well as in those with alarm features (vomiting, gastrointestinal bleeding, anemia, abdominal masses, unexplained weight loss, or progressive dysphagia).

### POINTS DE REPÈRE DU RÉDACTEUR

- Le reflux gastro-œsophagien (RGO) peut être diagnostiqué à partir des seuls symptômes, sans test diagnostique additionnel. La définition de Montréal du RGO décrit une approche fondée sur les symptômes et centrée sur le patient.
- La réponse à un traitement suppressif—inhibiteurs de la pompe à protons et antagonistes des récepteurs histaminiques H<sub>2</sub>—permet de diriger le traitement. Pour un patient donné, la corrélation entre le résultat de l'endoscopie et la gravité des symptômes peut être faible.
- Une endoscopie devrait être envisagée chez ceux qui ont symptômes de RGO fréquents et de longue durée (plus de 5 ans) afin d'éliminer un œsophage de Barrett, ainsi que chez ceux qui présentent des signes inquiétants (vomissements, saignements digestifs, anémie, masse abdominale, perte de poids inexpliquée ou dysphagie progressive).

**SUPPLEMENTING DECLARATION**

**OF NIMISH VAKIL, MD**

**WITH ATTACHMENTS**

Customer No.: 26308

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Pettersson

Attorney Docket No.: 9404.20833

Serial No.: 10/475,254

Examiner: Susan T. Tran

Filed: December 12, 2003

Group Art Unit: 1615

Title: Gastric Acid Secretion Inhibition Composition

**SUPPLEMENTING DECLARATION OF NIMISH VAKIL, M.D., FACP, FACG**

1. I am Nimish Vakil, MD, FACP (Fellow of the American College of Physicians), FACG (Fellow of the American College of Gastroenterology). I am a certified, practicing physician, specializing in internal medicine and, in particular, in gastroenterology. Gastroenterology is a branch of medicine that treats disorders and diseases of the gastrointestinal tract (also called the digestive system).
2. I received my M.D. degree in internal medicine in 1982 from the University of Bombay (Seth G.S. Medical College), Bombay, India. From July 1983 to June 1985, I conducted my residency in internal medicine at New York Medical College Affiliated Hospitals, New York, New York. I received my certification from the American Board of Internal Medicine in 1985. From July 1985 to June 1987, I conducted my fellowship in Gastroenterology at the Northwestern University School of Medicine, Chicago, Illinois. I received my certification from the American Board of Gastroenterology in 1987.
3. Besides being a certified physician who has treated patients since 1985, I have been a professor of medicine on the faculties of the University of Texas, Houston, Texas (Assistant Professor: 1987-1988); University of Rochester, Rochester, New York (Assistant Professor: 1988-1993); University of Wisconsin, Madison, Wisconsin (Clinical

Associate Medicine: 1993-1997); University of Wisconsin Medical School, Madison, Wisconsin (Clinical Professor of Medicine: 1997 to the present); and the Marquette University College of Health Sciences, Milwaukee, Wisconsin (Clinical Associate Professor of Medicine: 2002 to the present) (dual appointment with the University of Wisconsin Medical School).

4. I attach my Curriculum Vitae (CV) (Attachment 1). My CV recounts my educational and professional experience and associations. My CV also lists my many peer-reviewed publications; book chapters; invited papers/editorial; and national and international professional assignments in the field of internal medicine and gastroenterology, which well exceed 200 in number. Recently, I have been honored by an official invitation to author a key chapter on peptic ulcer disease for the upcoming 9<sup>th</sup> Edition of Schlesinger and Fordtran's *Gastrointestinal and Liver Disease (Pathophysiology/Diagnosis/Management)*, which is the leading textbook (the professional "bible") in the field of gastroenterology.

5. An area of personal and professional interest, experience, and expertise for me as a physician and educator within the field of gastroenterology is in the treatment of the disease called gastro-esophageal reflux disease (GERD). I have studied the medical literature and myself written extensively on the subject, having, since 2000, authored or co-authored over 30 publications directed to the pathophysiology, diagnosis, and management of GERD (these are listed in my CV). My personal and professional interest, experience, and expertise in this area are recognized by my colleagues. Further details of my personal and professional interest, experience, and expertise are set forth in my prior Declaration (paragraphs 1 to 7) submitted in related United States Patent Applications Serial Nos. 10/531,598 and 11/544,750 (Examiner Micah-Paul Young, Group Art Unit 1618), a copy of which has also been submitted in the present Application Serial No. 10/475,254. I incorporate by reference the opinions expressed in my prior Declaration into this Supplementing Declaration.

6. I have been asked to comment further in this Supplementing Declaration about the discovery made Anders Pettersson, M.D at Orexo in 2001 of a method for the treatment of symptoms of gastro-esophageal reflux disease (GERD), of which I am personally familiar and have studied. The method administers in an oral dosage form a proton pump inhibitor or a salt thereof (PPI) in combination with an H2 receptor antagonist or a salt thereof (H2RA), together with a pharmaceutically acceptable carrier and an enteric coating on the PPI that separates the PPI from the H2RA. The PPI and H2RA (separated by an enteric coating) are co-administered concurrently. In shorthand, I will refer to this discovery by Dr. Pettersson as the "Invention."

7. I understand that the Invention and related discoveries are the subject of pending United States Patent Applications, among them Serial No. 10/475,254; Serial No. 10/531,598; and Serial No. 11/544,750. In Serial No. 10/531,598 and Serial No. 11/544,750, I prepared a Declaration presenting my opinion as a person of ordinary skill in the art, that I and my colleagues would not have been motivated by the teachings and suggestions of the published literature to treat GERD by combining an H2RA and PPI for co-administration. In that Declaration, I stated my opinion that the co-administration of an H2RA and a PPI is inconsistent with what my colleagues and I in the field believed at a time prior to the Invention. This Declaration has also been filed in the present United States Patent Application Serial No. 10/475,254.

8. In the present application, I understand that the United States Patent Office has taken the position to the effect that a person of ordinary skill in the art at a time prior to the Invention would have understood the term "antacid" to encompass a PPI. I respectfully challenge this assessment, because it is inconsistent with the teachings of the published literature about the pharmacological treatment options for GERD that were available prior to the Invention. In short, my colleagues and I at a time prior to the Invention who read the peer literature, who wrote about and studied the pharmacological treatment options for GERD, and who treated patients with GERD understood that an

“antacid,” by legal and scientific definition, cannot be considered a PPI or any other form of anti-secretory drug. I will explain why.

9. In this Supplementing Declaration, I will comment in greater detail about the differences between antacids, on one hand, and anti-secretory drugs, on the other hand, from both a historical and scientific perspective, as considered from the viewpoint of a person who has spent over twenty years in the field of gastroenterology and related pharmacology. I do so, because I think this perspective provides the basis for understanding why a person of ordinary skill in the art at a time prior to the Invention would not consider the term “antacid” to encompass, by any legal or scientific definition, a PPI or any other form of anti-secretory drug. From both a historical and scientific perspective, there is no question that, at a time prior to the Invention, my colleagues and I considered an antacid and an anti-secretory drug like PPI to being pharmacologically distinct and mutually exclusive categories of drugs.

10. As the above summary of my background indicates, and as further related in my prior Declaration, I am a person who has considerable interest, experience, and expertise in the physiology of gastric secretion in the human stomach, the physiology of GERD, and the pharmacology of the drugs that have been used to treat the disease in the years prior to the Invention. As a professor, I teach others in these matters at medical schools. As a medical doctor, I have myself authored many peer-reviewed articles on these matters, and I have read many peer-reviewed articles and textbooks written by my colleagues. I regularly attend (and I am honored to sometimes chair) professional conferences where these matters are openly discussed and debated among my fellow doctors and scientists. This is the way professionals in my field share our scientific and clinical interests, experiences, and expertise pertaining to GERD and its treatment. I think these traits characterize professionals like me and my colleagues who practice in the field of gastroenterology and related pharmacology, so when I speak for myself, I am speaking for my colleagues in general.

11. To appreciate my state of mind and the state of mind of my colleagues a time prior to the Invention, one must understand how we treated GERD at that time (as I described in detail in paragraphs 14 to 26 of my prior Declaration); what my colleagues and I believed at the time about the cellular mechanism for gastric acid secretion in the stomach (as I described in detail in paragraphs 27 to 34 of my prior Declaration); and what we at that time understood how antacids functioned (as I described in paragraphs 15 and 16 of my prior Declaration), as distinguished from how we at that time understood how the anti-secretory drugs like H2RA's and PPI's functioned (as I described in detail in paragraphs 35, 36, and 37 of my prior Declaration). These views remain current today.

12. I have studied and written about the pharmacological treatment options that were available to me to treat my GERD patients in 2000. These included (i) antacids; (ii) H2RA's; and (iii) PPI's. (see American Journal of Gastroenterology, Vol. 96, No. 2, 2001. pp. 309) (Attachment 2). My colleagues and I in the field knew at that time (and today) that antacids, H2RA's, and PPI's are distinctively different pharmaceutical agents. They work in distinctively different ways. An antacid is, by legal and scientific definition, not an H2RA or a PPI, and vice versa.

13. My colleagues and I in the field knew at that time (and today) that antacids are drugs that simply neutralize gastric acid after it has been secreted by parietal cells in the stomach. Chemically, they are weak bases -- such as sodium bicarbonate, magnesium hydroxide, or aluminum hydroxide. Antacids are the original, classic remedies for the afflictions called "sour stomach" or "acid stomach" or "heart burn." Antacids have been used for decades, and perhaps even centuries, for these afflictions. They are described in old English literature. The "patent medicine" remedies for an "acid stomach" in the 1910's and 1920's were the antacid bicarbonate of soda. Antacids were used to treat an "acid stomach" or "heart burn" long before the medical community even understood what GERD really is. The trademarks for popular antacids -- ROLAIDS® or TUMS® or MAALOX®-- are ingrained in our popular lay lexicon.



14. I want to provide further insight into antacids from a historical perspective, because it demonstrates why my colleagues and I view as fundamental and important the differences between antacids, on one hand, and the anti-secretory drugs, on the other hand, which came about much later in time. For decades (up to about 1972), antacids were the only effective pharmaceutical remedy for inhibiting acid in the stomach. Everything that relieved stomach acid at that time was generically called an “antacid,” because that is what it was, and there was nothing else to call it. Gastroenterology was therefore preoccupied with the science and terminology of “antacids.” An informative historical account in the peer literature calls this the “acid era.” (see M. Schubert et al., “Control of Gastric Acid Secretion in Health and Disease,” *Gastroenterology* 2008; 134: 1842-1860, p. 1842) (Attachment 3), a time when antacids were dispensed “not by the bottle, by the case.” The authors recount:

“Is the study of gastric acid now only of historical interest? Many have forgotten the central role acid played in shaping gastroenterology as a specialty. It was in the acid era that our specialty was defined and flourished. Acid was meticulously measured in an attempt to better understand and treat peptic ulcer disease, the major clinical challenge at that time. Fiberoptic endoscopy was developed to better define upper gastrointestinal acid-related mucosal damage. Acid neutralization consumed clinicians. Antacids were dispensed, not by the bottle, but by the case. Neutralizing capacity, taste, sodium content, and adverse effect profile (diarrhea or constipation) of the various antacids were hot issues debated at national meetings because, to adequately control acid, antacids were dosed 1 and 3 hours after meals and at bedtime. Anticholinergic medications, despite their associated adverse effects, were prescribed before meals and at bedtime to prolong gastric emptying of antacids and to control nocturnal ulcer symptoms. Gastric freezing and radiation were modalities employed to reduce acid in patients with ‘medically refractory’ symptoms when surgery was not a consideration. Peptic ulcer surgery was planned based on gastric acid output measurement: high acid secretion generally indicated a more extensive resection. Too much postoperative acid (incomplete vagotomy) meant ulcer recurrence, whereas too little acid (large resection) had nutritional

consequences. Milk alkali syndrome, gastric outlet obstruction, and dumping syndrome, complications largely unknown to today's gastroenterology fellows, were common occurrences. All this characterized the 'BC' (before cimetidine) era of gastroenterology."

15. In 1972, all this changed. The "C" in "BC" that marked the end of the acid era, is cimetidine. Cimetidine is the first of the anti-secretory drugs. Cimetidine is an H<sub>2</sub>RA. It does not neutralize gastric acids after it is secreted into the stomach like an antacid, but works by an altogether different mechanism: it blocks the action of histamine in parietal cells to inhibit the secretion of gastric acid in the first instance (see my prior Declaration, paragraphs 17 and 35 for greater detail). Cimetidine is now referred to in the popular lexicon by its tradename Tagamet®.

16. It was Sir James Black who discovered cimetidine in 1972. This discovery was a breakthrough in the field of gastroenterology. It marked the end of the "acid era." So dramatic was the discovery that Sir James Black was awarded the Nobel Prize for Medicine, which was only the second time a Nobel Prize had been awarded in the field of gastroenterology. The discovery of the first anti-secretory drug shared the stage of history with award in 1904 of the Nobel Prize in the field of gastroenterology to W. Prout for discovering the presence of inorganic hydrochloric (gastric) acid in the stomach and I.P. Pavlov for the discovery of the neuro-reflex stimulation of secretion of gastric acid (who we memorialize in the popular story known to every school child as "Pavlov's Dog"). Persons of ordinary skill in the art recognized that Sir James Black's discovery of the first anti-secretory drug cimetidine "changed the practice of gastroenterology forever." (see M. Schubert et al., "Control of Gastric Acid Secretion in Health and Disease," *Gastroenterology* 2008; 134: 1842-1860, p. 1842) (Attachment 3):

"Sir James Black's Nobel Prize winning discovery of H<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs) in 1972 shed new light on acid secretion and changed the practice of gastroenterology forever. For the first time, acid could be inhibited and ulcers predictably healed. Studies showed that the duration and degree of acid inhibition (percentage of the

day pH >3) determined ulcer healing, and once daily dosing of H2RAs at bedtime was the most efficient healing regimen. In addition, continuous bedtime administration of the medication could prevent ulcer recurrence, the first step in controlling this chronic condition.”

17. The discovery of anti-secretory drugs even changed the practice of surgery in the field of gastroenterology. In the antacid era – the “BC” (before cimetidine) era – ulcer surgery constituted 50% to 70% of all surgical procedures performed in the United States. Since the discovery of anti-secretory drugs, ulcer surgery accounts for only a handful of surgical procedures in the United States each year.

18. The discovery of other anti-secretory H2RA drugs followed in the 1970’s -- for example, ranitidine (Zantac®) and famotidine (Pepcid®). Zantac® became the best selling drug in the world. The anti-secretory proton pump inhibitor drugs, known as PPI’s, emerged a decade later. The anti-secretory PPI drugs -- which include omeprazole (Prilosec®), esomeprazole (Nexium®) and lansoprazole (Prevacid®) – also act by an altogether different mechanism than antacids (and H2RA’s), by irreversibly binding to the H<sup>+</sup>,K<sup>+</sup>-ATPase enzyme (the proton pump) in parietal cells, to inhibit the secretion of gastric acid (as explained in more detail in my prior Declaration, paragraphs 36 and 37).

19. The anti-secretory PPI drugs proved to be more potent inhibitors of gastric acid secretion than H2RA’s. In the eyes of persons of ordinary skill in the art, the discovery of PPI’s stood out as a further breakthrough in the field of gastroenterology. The PPI Prilosec® supplanted the H2RA Zantac® as the best selling drug in the world.(see M. Schubert et al., “Control of Gastric Acid Secretion in Health and Disease,” *Gastroenterology* 2008; 134: 1842-1860, p. 1842) (Attachment 3):

“More recently, the identification of hydrogen-potassium-stimulated adenosine triphosphatase (H<sup>+</sup> K<sup>+</sup>-ATPase) as the proton pump of the parietal cell and *Helicobacter pylori* (HP) infection as the main cause of gastric and duodenal ulcer (also Nobel Prize

winning) heralded a new revolution in our understanding and treatment of acid-peptic disorders. Dosed before mealtime, proton pump inhibitors (PPIs) are the most effective acid inhibitors currently available and are the most widely prescribed class of gastrointestinal medications. Not only can peptic ulcers be healed more rapidly with PPIs, but refractory ulcers have all but disappeared. Eradication of HP with antibiotics, offered, for the first time, a permanent cure for most ulcers.”

20. When viewed from this historical perspective, one can readily appreciate that, in my mind and those of my colleagues, the replacement of classic antacid therapy with the breakthrough therapies using the anti-secretory drugs like H2RA's and PPI's is indelibly ingrained in our collective memories. In my mind and the minds of my colleagues, the switch from antacids to anti-secretory drugs was revolutionary. The advancement from antacids to anti-secretory drugs is historically stark and clear. It is marked by a change in patient treatment eras BC (the era of the antacids) to post BC (the era of the anti-secretory drugs); it is punctuated by the award of a Nobel Prize that highlights how drastically different the anti-secretory drugs were from their predecessors the antacids; and it led to revolutionary changes in the practice of medicine in the gastroenterological field. (see M. Schubert et al., “Control of Gastric Acid Secretion in Health and Disease,” *Gastroenterology* 2008; 134: 1842-1860, p. 1854) (Attachment 3):

“Gastric acid remains an important pathogenic factor for a variety of common upper gastrointestinal disorders. Over time, the prevalence as well as the management of these disorders has changed. Generations of gastroenterologists and surgeons measured acid output and tailored medical and surgical treatment of peptic ulcer disease based on the results. The management of these disorders has been revolutionized by the introduction of potent antiseccrory medications and the understanding of the role of HP in their pathogenesis. As a result, the quantitative measurement of gastric acid secretion, for the most part, has become obsolete ...”

21. With the discovery of the anti-secretory drugs, antacids were no longer the only effective pharmaceutical remedy for inhibiting acid in the stomach. Revolutionary new treatments had been discovered, effectively replacing antacids. Like the Nobel Prize awarded to Sir James Black, the peer literature, and persons of skill in the art who read the peer literature, likewise differentiated, compared, and contrasted between the classic antacids, on one hand, and the revolutionary antiseecretory drugs, on the other hand. My colleagues and I recognized that everything that relieved stomach acid could no longer be generically called an "antacid." For example, while Dr. Malagelada and his colleagues in 1979 recognized a "common goal" in the use of antacids or antiseecretory drugs, they also recognize the "different mechanisms" that the two agents employ (see Malageldal et al, "Antacid Therapy," *Scand J. Gastroenterol Suppl*: 1979; 55: 67-83, p. 72) (Attachment 4):

"Antacids, of course, neutralize acid which has already been secreted as opposed to other agents such as cimetidine or anticholinergics which inhibit acid secretion. Despite different mechanisms, as far as duodenal ulcer is concerned, all these different therapies have a common goal, namely to reduce duodenal acid load."

While recognizing a "common goal," Dr. Malageldal and his colleagues recognize that the use of antacids or anti-secretory drugs lead to different therapies having different clinical advantages and disadvantages in terms of outcomes and effects. Dr. Malageldal and his colleagues recognize that a clinician has to affirmatively decide whether to use antacids or to use anti-secretory drugs (that they are not interchangeable), concluding (see Ibid):

"Because of these advantages and disadvantages for each therapy, choosing one or the other must remain, for the present time, an individualized decision for the physician and his patient."

22. In a peer literature article written in 1977 (see Deering et al, "Comparison of an H2 Receptor Antagonist and a Neutralizing Antacid on Postprandial Acid Delivery Into the Duodenum in Patients with Duodenal Ulcer," *Gastroenterology* 73: 11-14, 1977, pp. 11 and 13) (Attachment 5), the authors (both MD's) call antacids and the anti-secretory H2RA drugs "radically different" and constituting "completely different mechanisms," writing:

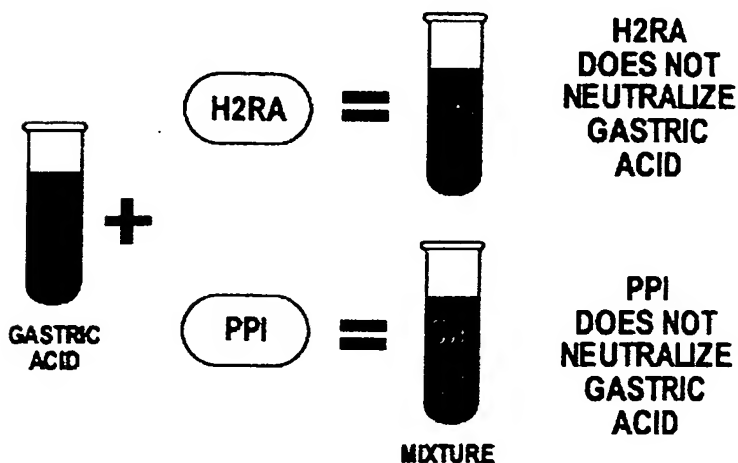
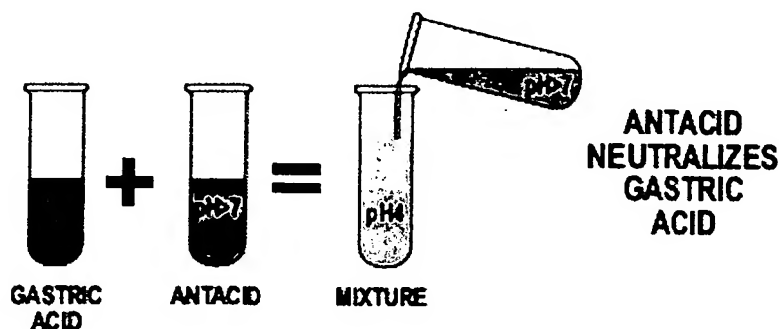
"Even seasoned skeptics are beginning to accept the possibility that histamine H2 receptor antagonists will revolutionize the therapy of peptic ulcer disease. If so, will H2 antagonists replace liquid neutralizing antacids in the standard ulcer regimen? We have compared the effect of these two radically different drugs on the postprandial delivery of acid into the duodenum of patients with duodenal ulcer, under experimental circumstances closely resembling physiological conditions... Cimetidine [an anti-secretory histamine H2 receptor antagonist) and Maalox [an antacid] reduce the acid entering the duodenum by completely different mechanisms. The histamine H2 receptor antagonist inhibits the secretion of gastric acid. In contrast, the aluminum and magnesium hydroxides in the liquid antacid neutralize acid that has already been secreted by the stomach, therefore, the acid delivered into the duodenum is that which remains unneutralized by the antacid."

23. The United States government agency responsible for pharmaceuticals – the Federal Food and Drug Administration (FDA) – also adopts the scientific distinction between antacids and the anti-secretory drugs found in the peer literature. The FDA has adopted as its legal and scientific regulatory definition for “antacid” a definition that reflects the historical and scientific views of persons of skill in the art, as described above. What constitutes (and, conversely what does not constitute) an antacid was identified prior to the Invention by the FDA in Title 21 U.S.C. § 331.11 (Food and Drugs) (1974) (Attachment 6). The FDA definition includes long lists of substances that correspond to the classic antacids of the earlier acid era, and also more generically characterizes antacids by their “acid neutralizing capacity” (21 U.S.C. § 331.10). The FDA further directs the use of an *in vitro* methodology for measuring the “acid neutralizing capacity” of an antacid (see 21 U.S.C. § 331.25 and 21 U.S.C. § 331.26). The *in vitro* tests specified by the FDA to identify an antacid are performed outside of the body in a beaker on a laboratory bench. The use of “acid neutralization” by the FDA to define an antacid is entirely consistent with the historical definition of an antacid prior to the Invention, as described above (see “neutralizing capacity” in the quote in Paragraph 14, *supra*). The *in vitro* evaluation of antacids to identify their acid neutralizing capacity is also reported in the peer literature prior to the Invention (see Malagelda et al, “Antacid Therapy,” *Scand J. Gastroenterol Suppl*: 1979; 55: 67-83, p. 68) (Attachment 4).



24. Inherent in the FDA's definition of an antacid and the historical and scientific definition of an antacid found in the peer literature, is that antacids can be demonstrated to work *in vitro* to neutralize gastric acid when poured into a beaker outside the body, just as they work inside the stomach (*in vivo*) to neutralize gastric acid secreted in the stomach. Else wise, the *in vitro* test for acid neutralization could not be used. In contrast, the anti-secretory drugs H2RA and PPI do not work *in vitro*, and therefore, by the definition existing prior to the Invention, cannot be an antacid. As illustrated schematically below, when placed into a beaker of gastric acid, no anti-secretory drugs (H2RA or PPI) will change the pH of the gastric acid. The anti-secretory mechanisms of an H2RA and PPI operate only *in vivo* within a functioning parietal cell.

**Schematic Representation of Difference Between  
Antacid and H2RA/PPI**



25. By definition, the legal and scientific definition of an antacid in the peer literature and by the FDA, as a substance having an "acid neutralizing capacity," excludes all anti-secretory drugs (both H2RA's and PPI's).

26. In other publications circulated prior to the Invention as well, the FDA defines antacids in terms of an acid neutralization capacity that neither H2RA's nor PPI's possess. For example, in Health Publications distributed by the FDA to consumers, the FDA asks the question "What's an Antacid" and answers the questions in terms of acid neutralization, writing (see Cramer, "What's an Antacid?", *FDA Consumer*, Jan-Feb, 1992, Attachment 7):

"The opposite of an acid is a base, and that's exactly what antacids are,

"But a base all by itself can't neutralize the acid inside you. For reasons that are best explained on a blackboard in chemistry class, a base needs some chemical helpers," or ingredients, to accompany it on its neutralizing mission into your stomach. All antacids contain at least one of the four primary "helpers" or ingredients: sodium, calcium, magnesium, and aluminum."

27. The FDA also recognizes prior to the Invention that there are significant differences between antacids and anti-secretory drugs in terms of the use of these drugs in the management of heartburn in pregnancy. In 1985, the FDA divided the safety of drugs used during pregnancy into five categories (A, B, C, D, and X), based upon systemic absorption and reports of congenital defects in animals or humans. (see Richter, "Review Article: The Management of Heartburn in Pregnancy," *Aliment Pharmacol Ther* 2005; 22: 749-757, p. 751) (Attachment 8). Antacids are not included in this rating system. However, H2RA's are rated FDA Category B drugs (animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women). The PPI omeprazole is rated as a FDA Category C drug (animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of

the drug in pregnant women despite potential risks). Other PPI's (e.g., lansoprazole and rabeprazole) are rated FDA Category B drugs.

28. I am aware that McGrew et al United States Patent 6,949,264 contains a paragraph (column 7, lines 32 to 38) (Attachment 9) that reads:

“Antacids include cimetidine, ranitidine, nizatidine, famotidine, omeprazole, bismuth antacids, metronidazole antacids, tetracycline antacids, clarithromycin antacids, hydroxides of aluminum, magnesium, sodium bicarbonates, calcium bicarbonate and other carbonates, silicates, and phosphates.”

This paragraph appears in the context of a disclosure directed to delivering medications incorporated into chewing gum.

29. At a time prior to the Invention, my colleagues and I would recognize McGrew's definition of “antacids” as lacking any scientific or clinical credibility. On the face of it, McGrew's definition of antacids includes the antibiotics metronidazole, tetracycline, clarithromycin, which even a lay person would recognize as being incredible. Furthermore, given the momentous history surrounding the discovery of anti-secretory drugs and the scientific distinctions uniformly drawn in the peer literature (also reflected in the FDA's definition), my colleagues and I would equally consider the inclusion of H2RA's (cimetidine, ranitidine, nizatidine, famotidine) and PPI's (omeprazole) as an “antacid” to be so preposterous as to exclude McGrew from any consideration as a valid scientific reference.

30. I am also aware that Vertesy et al. US 6,077,830 contains a sentence (column 11, lines 26 to 30) (Attachment 10)

“Triple therapy can thereby be simplified to dual therapy, in which beside the bismuth salt according to the invention, for example, only an antacid (for example omeprazole, lansoprazole, pantoprazole or others) is administered.”

It is my opinion that Vertesy et al, when taken in its full context, demonstrates that this sentence is likely a typographical error. Vertesy et al. in the next paragraph correctly refers to omeprazole, lansoprazole, pantoprazole as being a “proton pump inhibitor” (column 12, lines 26 to 28):

“A preferred combination contains the bismuth salts according to the invention together with a proton pump inhibitor such as, for example, omeprazole, lansoprazole, pantoprazole or others.”

Earlier in the same paragraph (column 12, lines 6 to 13), Vertesy correctly refers to the antacids group, and does not include in this group PPI's and H2RA's.:

“For the therapeutic and prophylactic uses mentioned, suitable additional active compounds derive, for example, from the antacids group, such as, for example, sodium bicarbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, aluminum magnesium silicate hydrate, aluminum sodium carbonate dihydroxide, magnesium carbonate, calcium carbonate or hydrotalcite.”

Vertesy et al. in Column 1, lines 42 to 47, also correctly identifies omeprazole as a “proton pump inhibitor”:

“The therapeutic aim is the complete eradication of *H. pylori* in the stomach. The therapy of choice is at present a triple combination which consists of a so-called acid inhibitor, for example a proton pump inhibitor such as omeprazole, and two antibiotics, such as, for example, clarithromycin and amoxicillin.”

It is my opinion that Vertesy et al, taken in context, correctly demonstrates the clear distinction between antacids and the anti-secretory drugs found in the peer literature and recognized by my colleagues and I.

31. I also note a later patent application that names as inventors many of the same inventors listed on McGrew et al. This later patent application is Zyck et al US 2001/0021403 (Attachment 11). The subject matter of Zyck et al is an antacid coated chewing gum. This application for a later invention contains the scientifically and legally correct definition of “antacid.” (see Zyck et al., US 2001/0021403, paragraphs 0018 to 0050). This application for a later invention also expressly differentiates between an antacid, on one hand, and the anti-secretory drugs (H2RA’s and PPI’s), on the other hand (see Zyck et al., US 2001/0021403, paragraphs 0051 to 0052):

“[0051] The preferred antacids are generally carbonate or hydroxide salts of calcium, magnesium or aluminum, and are generally very water insoluble. When these materials are mixed with acids in the GI tract, the acids are readily neutralized to give relief from GI disturbances. Neutralizing antacids, which are insoluble inorganic salts, are known to neutralize stomach acidity very quickly. As a result, relief from gastrointestinal distress is fast and effective, but does not last long, possibly up to about 30 minutes. An acid blocker, when taken in combination with the antacid, will start to be effective after about 30 minutes, and be most effective after about 3-6 hours, and may last up to about 9-12 hours.

“[0052] Examples of acid blockers are histamine H2 - receptor antagonists which include cimetidine, used in an over the counter (OTC) preparation called TAGAMET; famotidine, used in an OTC preparation called PEPCID; the

hydrochloride salt of ranitidine, used in ZANTAC; and nizatidine, used in AXID. Some other types of acid blockers are called gastric proton pump inhibitors. These include omeprazole, used in PRILOSEC, and rabeprazole. All of these have been used for the treatment of digestive disorders such as gastritis, dyspepsia, gastric hyperacidity, heartburn, gastric oppression and peptic ulcer.”

32. The Invention (identified by the drug designation OX17) has been clinically tested in a Phase II trial conducted by the assignee of the current application, Orexo AB. In a recent article “The Next Blockbuster Drugs” (*Newsweek*, July 22, 2009) (Attachment 12), OX17 is identified under the category of Heartburn Drugs as being a Potential Blockbuster (the only one so identified in this category):

“The Potential Blockbusters:

“There appear to be few significant near-term challengers on the horizon to the Nexium; the drug does not start coining off patent until 2015. But one company with a candidate that could be a contender is Orexo AB, with its OX17 proton pump inhibitor. It is being developed for the treatment of gastro esophageal reflux disease, the most serious form of acid reflux. It combines two substances in an effort to provide both long-lasting and fast-acting heartburn relief.

“In a Phase II trial last year, OX17 quickly proved effective in working fast and continuing to work to reduce stomach acid. Earlier this year, Orexo signed an exclusive development deal with a yet-to-be-named partner. The company expects to announce a licensing deal for its OX17 program this year, as well.”

33. In my prior Declaration (paragraphs 44 to 48), I reviewed the results of early clinical tests of the OX17 material. I noted the surprising and expected beneficial clinical results. I concluded then (and now):

"The Invention provides me and my physician colleagues a therapeutic tool that did not exist before. Surprisingly, the Invention has shown that it is appropriate, to co-administer PPI and H2RA together simultaneously or concomitantly in the dosage form and dosage regime as I have described. The data show that co-administration of H2RA and PPI simultaneously or concomitantly in this manner leads to a prompt beneficial additive relief of symptoms on Day 1, and persists for a prolonged treatment period, if necessary, on demand."

34. I have been warned that willful false statements and the like are punishable by fine, or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon. All statements I have made of my own knowledge are true, and all statements made upon information and belief are believed to be true.



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Nimish Vakil, M.D., FACP, FACG

Dated this 16 day of September, 2009.



# Curriculum Vitae.

Updated:1/09

**Nimish Vakil MD**  
**Clinical Professor of Medicine,**  
**University of Wisconsin School of Medicine and Public Health,**  
**Madison Wisconsin**

**Mailing address:**  
**W231 N1440 Corporate Drive, Suite 307,**  
**Waukesha WI 53186**  
**Telephone: 262-896-6400**  
**Fax: 262-896-8986**  
**E-mail: nvakil@wisc.edu**

## Faculty Appointments:

- University of Wisconsin Medical School, Madison, Clinical Professor of Medicine 7/1/97-present
- Marquette University College of Health Sciences, Clinical Associate Professor of Medicine, 2002-present
- University of Wisconsin                      Clinical Associate Professor                      7/1/93-6/30/97.
- University of Rochester                      Assistant Professor                      1988-1993.
- University of Texas                      Assistant Professor                      1987-88.

## Post-graduate Training:

- Northwestern University School of Medicine, Chicago, Illinois. Fellowship-Gastroenterology. July 1985-June 1987.
- New York Medical College Affiliated Hospitals, New York, New York-Internal Medicine Residency, July 1983-June 1985.
- University of Munich; Germany, Advanced Endoscopy under Professor M. Classen, Federal Republic of Germany; July 1987- October 1987.

## Medical School:

University of Bombay, Seth G.S. Medical College, Bombay, India

- MBBS 1980;
- MD (Internal Medicine) 1982.

**Certification:**

- American Boards of Gastroenterology, 1987
- American Boards of Internal Medicine, 1985
- Wisconsin license, # 34096

**Professional Organizations:**

- Fellow, American College of Gastroenterology.
- Fellow, American College of Physicians
- American Gastroenterological Association
- American Society for Gastrointestinal Endoscopy

**Editorial Responsibilities:**

2003 onwards: Associate Editor, American Journal of Gastroenterology  
2006 Onwards: US Editor, Endoscopy

**Editorial Boards:**

2002-present. International Editorial Board, Alimentary Pharmacology and Therapeutics  
2000- present. Editorial Board, Evidence based Gastroenterology  
2000-present. Editorial Board, Digestive and Liver Disease  
1999-2004. Editorial Board, American Journal of Gastroenterology

**Patient related Organizations:**

- Advisory Board, International Foundation for Functional Bowel Disorders, Milwaukee WI.
- Advisory Board, Cyclical Vomiting Association

**Honors and Awards:**

- 1998: Northwestern University Alumnus Award awarded May 1998 at the American Gastroenterological Association, New Orleans LA
- 1995: European H Pylori Study group, Edinburgh, Scotland. July 1995- First Prize for original research paper- Decision Analysis of the Economic Impct of Helicobacter Pylori eradication regimens.
- 1995: Certificate of appreciation from the American Society of Gastrointestinal Endoscopy for chairmanship of the ad hoc committee on networking.
- 1994: American Gastroenterological Association Junior Faculty Travel Award to the World Congress of Gastroenterology-1994.
- 1991: German Academic Exchange Research Study Award, Universities of Munich and Kassel, Germany.
- A Blaine Brower Traveling Fellowship of the American College of Physicians:  
- University of Munich, W Germany
- Chicago Gastroenterology Fellows Research Prize 1987.
- 1985: American College of Physicians Clinical Vignette Prize 1985.

## **Publications:**

### **Internal Medicine Journals:**

1. VAKIL N, VAIRA D. Sequential therapy for *Helicobacter pylori*: time to consider making the switch? *JAMA*. 2008 Sep 17;300(11):1346-7.
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7. VAKIL N. Functional dyspepsia: the devil in the details. *Am J Med*. 2004 Jun 1;116(11):781-2.
8. VAKIL N, KIRBY R, SHAW M. Clinical effectiveness of laparoscopic fundoplication in a US community. *Am J Med* 2003 Jan;114(1):1-5
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13. TALLEY N, VAKIL N, BALLARD C, FENNERTY B. Effect of eradicating *Helicobacter pylori* in patients with non-ulcer dyspepsia. *New England J Med* 1999;341:1106-11.
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### *National and International Professional Assignments:*

- Chair Quality of life Abstract review committee DDW 2008
- Dyspepsia, Quality of life review committees DDW 2007
- Chair Dyspepsia abstract review DDW 2006
- Chair Dyspepsia abstract review DDW 2006
- Chair Dyspepsia review section DDW 2004
- Associate Chair H pylori section DDW 2003
- 1998-2002: Chairman, Practice Parameters Committee, American College of Gastroenterology

- 2000-present: Publications and Guidelines Committee of the Organisation Mondiale de Gastroenterologie
- 2000-2001: Technology assessment committee of the American Society for Gastrointestinal Endoscopy
- DDW 2000: Associate Chair, H pylori section for DDW abstracts
- 1998-2000: Member, National Affairs Committee, American College of Gastroenterology
- 1998-2000: Member, Research Committee, American College of Gastroenterology
- 1993-4, 1994-5, 1995-1997, 1998-2000: Member, Medical Informatics Committee of the American Society of Gastrointestinal Endoscopy
- 1995-6, 1996-7, 1997-8: Member Practice Parameters Committee of the American College of Gastroenterology.
- 1993-4, 1994-5: Chairman, National Committee of the American Society of Gastrointestinal Endoscopy on "Networking in endoscopy".
- 1994-1995, 1995-1996: Health Information Technology sub-committee of the American Society for Parenteral and Enteral Nutrition.

# Nonerosive Reflux Disease— Current Concepts and Dilemmas

Ronnie Fass, M.D., M. Brian Fennerty, M.D., F.A.C.G., and Nimish Vakil, M.D., F.A.C.G.

*Section of Gastroenterology, Southern Arizona VA Health Care System and University of Arizona Health Sciences Center, Tucson, Arizona; Division of Gastroenterology, Department of Medicine, Oregon Health Sciences University, Portland, Oregon; and Section of Gastroenterology, Department of Medicine, University of Wisconsin Medical School, Milwaukee, Wisconsin*

## ABSTRACT

Nonerosive reflux disease is defined as the presence of typical symptoms of gastroesophageal reflux disease caused by intraesophageal acid in the absence of visible esophageal mucosal injury at endoscopy. Recent studies demonstrate that it is a chronic disease with a significant impact on quality of life, and it is very common in primary care settings. Treatment with acid inhibitory agents is effective, and proton pump inhibitors are the most effective form of therapy. (*Am J Gastroenterol* 2001;96:303–314. © 2001 by Am. Coll. of Gastroenterology)

## INTRODUCTION

Symptoms of gastroesophageal reflux disease (GERD) such as heartburn and acid regurgitation occur weekly in 20% of the adult population (1). The prevalence of reflux symptoms probably underestimates the true prevalence of GERD, as it is based solely on the presence of heartburn and/or acid regurgitation. Recent data indicate that many patients with GERD present with symptoms such as acid reflux–related chest pain (noncardiac chest pain), asthma, cough, and hoarseness, and lack concomitant symptoms of heartburn or acid regurgitation (2). For instance, it has been demonstrated that as many as 60–70% of adult asthmatics have GERD. Given the prevalence of asthma in the adult population in the United States as well as the millions of patients with noncardiac chest pain, cough, and hoarseness, the true prevalence of GERD is likely to be substantially greater than 20%.

Until recently our understanding of GERD was largely limited to patients with erosive esophagitis. Investigators and clinicians were concerned with erosive esophagitis for a number of reasons. Foremost among these was the need for an unequivocal criterion for the diagnosis of gastroesophageal reflux disease in clinical trials. This resulted in most of the literature on therapy being limited to patients with erosive esophagitis. The presence of erosive esophagitis also provided an objective means of measuring efficacy, as heal-

ing could be clearly defined. These trials fostered the development of numerous scoring systems of esophagitis (3, 4) furthering interest and limiting the focus of research in GERD to patients with erosive esophagitis. Compounding this research “bias” toward GERD patients with erosive esophagitis was the erroneous belief that the adverse clinical impact of GERD was limited to those with erosive esophagitis. This belief ignored accumulating data that the greatest clinical impact of GERD was on quality of life (QOL) and that the impairment was similar in patients with and without erosive disease (5). The assumption that therapeutic needs were not as great in patients with nonerosive reflux disease (NERD) has also been challenged by recent studies. NERD therefore represents an enormously important clinical problem that requires a refocus of our attention and a priority for clinical research.

In this article, we review what is known about the pathophysiology, diagnosis, and treatment of NERD, as well as its cost to society and to health care systems. We also identify critical areas where information is lacking, to shed further light on this enormously important clinical issue.

## DEFINITION

There is no generally agreed upon definition of NERD in the literature. We define NERD as the presence of typical symptoms of gastroesophageal reflux disease caused by intraesophageal acid, in the absence of visible esophageal mucosal injury at endoscopy.

It is clear that NERD is not composed of a homogeneous group of patients. The functional esophageal disorders committee that convened in Rome in 1990 suggested the use of 24-h esophageal pH monitoring as a tool to distinguish a subset of NERD patients as those with “functional heartburn” (6). Functional heartburn was defined as burning retrosternal discomfort for  $\geq 3$  months in the absence of pathological gastroesophageal reflux by 24-h esophageal pH monitoring and esophagitis by endoscopy. The committee suggested that further distinction between subgroups of functional heartburn patients could be achieved by correlating physiological acid reflux events with symptoms of heart-

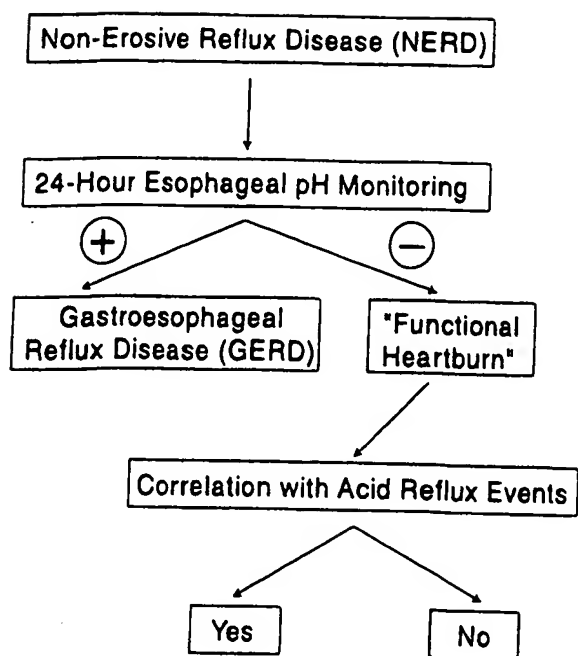


Figure 1. Subcategorization of the nonerosive reflux disease (NERD) group by using 24-h esophageal pH monitoring and "symptom index," as suggested by the functional esophageal disorders committee in Rome in 1990 (6).

burn (Fig. 1). As the pH test is not a gold standard for the diagnosis of GERD, it may not be reliable in categorizing the NERD group (Figs. 2-4). False negative results are not uncommon and may occur even in patients with documented erosive esophagitis (7, 8). Furthermore, it has been demonstrated that 30-50% of NERD patients presenting with heartburn will have no evidence of pathological acid reflux by currently available diagnostic modalities (6, 9, 10).

## EPIDEMIOLOGY AND NATURAL HISTORY

Gastroesophageal reflux disease represents a spectrum of symptoms and tissue damage. Patients may present with typical symptoms such as heartburn and acid regurgitation and/or atypical symptoms such as chest pain, hoarseness, and cough. In addition, patients may present with normal esophageal mucosa, mucosal inflammation, or complica-

tions such as stricture and Barrett's esophagus. It has been demonstrated that there is no correlation between the severity of GERD symptoms and the presence or absence of visible esophageal inflammation (11).

Early studies that originated from tertiary referral centers suggested that approximately half of the patients presenting with reflux symptoms had erosive esophagitis at upper endoscopy (11, 12). However, most patients with GERD either self-medicate and never seek medical attention, or they are seen and treated by community-based physicians (13). Recent studies that were carried out in community practice revealed that up to 70% of the GERD patients have NERD (14, 15). Therefore, erosive esophagitis does not seem to be as common as previously suggested. In another community-based study of antacid users, Robinson *et al.* found that 53% of GERD patients had NERD and two thirds of the remainder had only mild erosive changes at endoscopy (16). This study highlights another important finding that in community-based patients with esophageal mucosal injury, mild erosive esophagitis is the most prevalent form of mucosal injury.

Only a few studies, mostly retrospective, have assessed the natural history of NERD. In one study from Italy, 33 NERD patients were followed for a period of 6 months while on antacids and/or prokinetics (17). At the end of the follow-up period, 58% remained symptomatic and 15% had developed erosive esophagitis. A total of 42% became asymptomatic and were able to discontinue all medical therapy. There was no difference in the pattern of GERD between the symptomatic patients and those that became asymptomatic. However, this retrospective review offers only a short-term follow-up. In another study from Scotland, NERD patients with either excess or normal esophageal acid exposure but a positive symptom index were followed for a median period of 6.5 and 4.4 yr, respectively (18). In all, 87% of those with normal acid exposure and 79% of those with excess acid reflux remained symptomatic; 53% and 47%, respectively, recorded their symptoms as the same or worse than at the original presentation, despite regular use of medications in 60% of patients in each group. These studies and others suggest that most NERD patients will demonstrate a chronic pattern of symptoms with periods of exacerbation and remission. Further delineation of the clin-

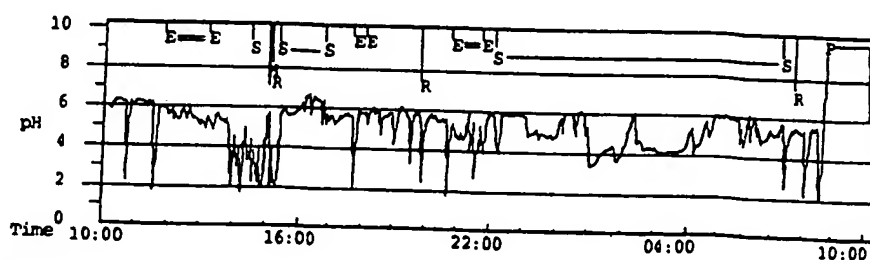


Figure 2. A 24-h esophageal pH recording in a patient with nonerosive reflux disease (NERD). During the test the patient experienced three episodes of acid regurgitation (R) and one episode of heartburn (H). All symptoms correlate with acid reflux events, suggesting a 100% symptom index. (E = meal; S = supine position.)

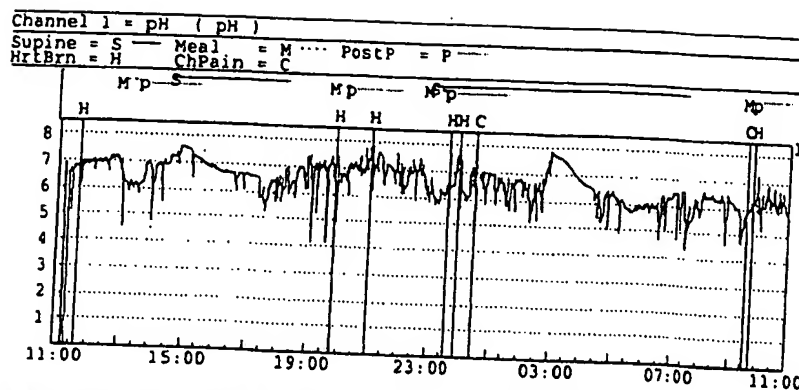


Figure 3. A 24-h esophageal pH recording in a patient with nonerosive reflux disease (NERD). Despite the lack of any acid reflux events, the patient reported six episodes of heartburn (H) and two of chest discomfort (C). Calculated symptom index is 0%.

ical characteristics of NERD patients over a longer period is needed.

### MECHANISMS OF HEARTBURN

Heartburn is the classic symptom of GERD that is perceived by patients with and without mucosal injury. In patients with erosive esophagitis, stimulation of sensory afferent pathways by acid refluxate or inflammatory mediators is considered to be the mechanism underlying symptom generation. The precise relationship between symptoms of heartburn and acid reflux events in patients with normal endoscopy remains to be established.

There is evidence for the presence of nerve terminals of both vagal and spinal fibers within the mucosa and muscle layer of the esophagus (19–22). However, the precise localization of specific intramural nerve structures that are responsible for the transmission of painfully perceived, afferent information is not yet known. It seems that activation of peripheral terminals of spinal rather than vagal afferents are a necessary condition (22). Polymodal vagal afferents with receptive fields in the esophageal mucosa are important in chemically or mechanically induced reflex regulation that is not associated with conscious perception under normal

conditions (19). Vagal afferents seem to have no role in visceral pain transmission, except for a pain-modulatory effect for certain types of vagal afferents and a role in perception of esophageal distension (23, 24). In contrast, spinal afferents are thought to be important for the transmission of discomfort and pain (25). The receptive fields for mechanosensitive spinal afferents are assumed to be located primarily in the muscle and serosa, whereas the intraepithelial nerve endings of spinal afferents are likely to be involved in the mediation of acid-induced pain during topical exposure to intraluminal acid (20).

The mechanisms that lead to symptoms of heartburn in patients lacking esophageal mucosal injury remain an area of intense research. In both animal models and humans, dilation of the intercellular spaces has been noted in acid-exposed tissues (26, 27). In humans, these findings were detected by transmission electron photomicrographs in patients with erosive and nonerosive reflux disease (27, 28). These findings may suggest that patients with reflux disease have an increase in paracellular permeability in the esophageal epithelium (29). Because sensory neurons in the esophageal epithelium reside within the intercellular spaces, the increase in paracellular permeability may explain heartburn symptoms during esophageal acid exposure in patients

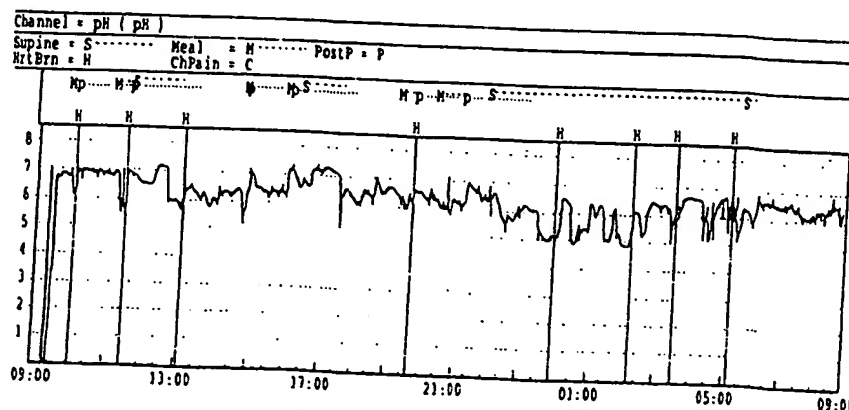


Figure 4. A 24-h esophageal pH monitoring in a patient with nonerosive reflux disease (NERD) who experienced eight episodes of heartburn (H). The heartburn episodes correlate very closely with minute changes in intraesophageal pH.

with NERD (29). However, this hypothesis provides only a partial explanation for the relationship between symptom generation and acid reflux events that has been observed in NERD patients.

It is currently accepted that an excess of intraesophageal acid and perhaps other components of duodenogastro-esophageal reflux are the primary causes for symptoms of heartburn in NERD patients. However, between 33% to 50% of the patients with NERD will have normal test results when they undergo initial 24-h esophageal pH monitoring, and up to 25% will reverse diagnosis (positive to negative test and *vice versa*) on subsequent pH testing (8, 14, 30–32). These data suggest that in a significant number of NERD patients, physiological acid exposure may be sufficient to cause typical symptoms of heartburn.

The specific role of the symptom index, which determines the percentage of symptoms that correlates with acid reflux events, remains to be elucidated in NERD (33). In addition, interpretation of a positive symptom index (>50%) in the setting of a normal pH test remains an area of controversy. Although some have considered it indicative of GERD (false negative pH test by conventional criteria), others have suggested that it might be indicative of a group of patients that is highly sensitive to physiological amounts of acid reflux (functional heartburn) (6, 9). Patients with abnormal upper endoscopy are more likely to experience heartburn symptoms (65%) during pH testing than patients with normal endoscopy and abnormal pH testing (32.5%) and those with both normal endoscopy and pH testing (21%) (34). In general, patients with erosive esophagitis are significantly more likely to have a positive symptom index when compared with NERD patients (33). Furthermore, patients with a normal upper endoscopy and 24-h pH test have a significantly lower calculated symptom index ( $26\% \pm 10.7\%$ ) than those with abnormal upper endoscopy ( $85\% \pm 4.6\%$ ) or normal endoscopy and abnormal pH testing ( $70\% \pm 7.1\%$ ). These data suggest that patients with a normal endoscopy and 24-h pH test are less likely to have an abnormal symptom index (34, 35). The symptom index data may mean that a subset of NERD patients with physiological acid reflux may have hypersensitivity to acid. It is also possible that other non-acid-related intraesophageal stimuli can trigger heartburn. Animal models of afferent nerve sensitization have demonstrated that acid exposure can sensitize esophageal nerve endings (chemoreceptors) directly or via inflammatory mediators, resulting in lower pain thresholds (36). The sensitized esophageal chemoreceptors are part of the spinal afferents, which mediate esophageal sensation. Altered pain perception demonstrated by increased chemoreceptor sensitivity to acid has been shown in NERD patients (37, 38). This hypersensitivity to acid can be demonstrated in both the proximal and distal esophagus (39). However, NERD patients seem to be less sensitive to acid when compared to patients with documented erosive esophagitis, regardless of their endoscopic grading (37, 40).

Assessment of mechanoreceptor sensitivity using intra-

esophageal balloon distension has yielded contradictory results. Trimble *et al.* evaluated patients with heartburn and excess reflux defined by abnormal upper endoscopy and/or 24-h esophageal pH monitoring and compared them to patients with heartburn and a normal 24-h pH test; the results demonstrated that the latter group had lower volume thresholds for perception of esophageal balloon distension and discomfort (41). This study suggests that patients with typical heartburn who lack any evidence of excess acid are highly sensitive to mechanical stimuli. In another study using esophageal balloon distension delivered by an electronic barostat, patients with NERD and erosive esophagitis did not demonstrate an increase in mechanosensitivity, when compared to normal controls (37).

The current literature suggests that there is a differential effect of long-term esophageal acid exposure on chemosensitivity and mechanosensitivity in humans. Chronic esophageal exposure to excess acid affects chemosensitive but not mechanosensitive afferent pathways. Only patients with typical GERD symptoms and no evidence of excess acid demonstrate an increase in mechanosensitivity. Some experts hypothesize that the latter group might be sensitive to minute changes in pH that do not reach our current criterion for acid reflux event ( $\text{pH} < 4$ ) (Fig. 4). Data to support this intriguing hypothesis are still lacking. Thus far, the axiom has been that pathological amount of acid is the only visceral stimulus that can result in heartburn ("no acid, no heartburn"). However, as has been mentioned, heartburn may be reported when the extent of esophageal acid exposure is within the physiological range in patients with either a negative symptom index or a complete absence of any documented acid reflux events (38). These data suggest that non-acid-related stimuli may produce heartburn as well in a subset of patients with NERD.

In a recent study it has been demonstrated that chest pain and heartburn may be provoked in normal subjects during esophageal balloon distension either in the proximal or distal portion of the esophagus (37). Interestingly, volume thresholds for heartburn and chest pain in both esophageal locations were similar, suggesting that for a specific volume some patients will develop chest pain and others heartburn. Furthermore, volume thresholds for both chest pain and heartburn did not differ significantly at each esophageal location and between locations. In this study, esophageal balloon distension also reproduced typical heartburn symptoms in patients with documented GERD who were being treated with high-dose proton pump inhibitors. This study clearly demonstrates that acid is not the only visceral stimulus that may lead to heartburn. Pehlivanov *et al.* suggested that longitudinal muscle contractions of the esophagus, detected only by high frequency intraluminal ultrasound and not by traditional esophageal manometry, are the motor equivalent of heartburn sensation (42). These contractions may occur in the presence or absence of acid reflux. This intriguing observation requires further confirmation.

The data discussed so far suggest that NERD patients





when compared with patients with heartburn who had a positive symptom index. Stress and psychological comorbidity seem to have an important role in symptom generation in patients with GERD and, in particular, those with NERD. This emerging concept suggests that by modulating brain-gut interactions, symptom perception and possibly pathological events in the esophagus of GERD patients might be altered.

Figure 6 is a conceptual model that summarizes the mechanisms that are responsible for the sensation of heartburn in patients with NERD. It is likely that patients with NERD are a heterogeneous group with different mechanisms responsible for their symptoms. Some patients experience heartburn caused by excess acid reflux; others demonstrate esophageal chemoreceptor sensitivity to physiological amounts of acid. Another subgroup of patients will develop heartburn symptoms as a result of non-acid-related intraesophageal stimuli (possibly motor events). The latter subgroup, despite the presence of typical heartburn, does not meet the criteria for our definition of NERD. Central factors such as stress and peripheral factors such as intraduodenal fat may enhance the perception of various intraesophageal stimuli and thereby modulate symptoms in patients with NERD.

### PHYSIOLOGICAL CHARACTERISTICS

Assessment of esophageal motor function in patients with NERD reveals minor motility abnormalities compared to normal subjects. Patients with NERD have a slightly higher rate of primary peristalsis failure, defined by nontransmitted contractions or peristaltic contractions that do not traverse the entire esophageal body (53). Similarly, the mean amplitude of contractions in the distal esophagus and the mean lower esophageal sphincter pressure are mildly reduced (53). NERD patients rarely demonstrate lower esophageal sphincter pressures <10 mm Hg in contrast to patients with documented erosive esophagitis.

Assessment of esophageal acid exposure is limited by the lack of a gold standard for diagnosing gastroesophageal reflux disease. By using ambulatory 24-h esophageal pH monitoring it seems that NERD patients in general have slightly higher mean acid exposure than normal subjects and significantly less acid exposure than patients with erosive esophagitis (54, 55). This relationship is also maintained when esophageal acid exposure is evaluated either in the erect or supine positions (56).

By using the Bilitec 2000 (Medtronic, Minneapolis, MN), which detects bilirubin pigment spectrophotometrically, duodenogastroesophageal (DGER) reflux has been assessed in patients with GERD (57). The combination of both acid reflux and DGER correlated well with severity across the GERD spectrum. Esophageal exposure to both acid and DGER occurred in 50% of NERD patients as compared to 79% of patients with erosive esophagitis, 89% with uncomplicated Barrett's esophagus, and 100% of those with com-

plicated Barrett's esophagus. Further research concerning the role of DGER in NERD patients is needed.

### INVESTIGATION

In patients presenting with heartburn, unless alarm symptoms (such as dysphagia, bleeding, or weight loss) are present, empirical therapy is currently considered the standard of care (58). Using high-dose proton pump inhibitors (PPIs) for a short time, the PPI therapeutic trial as an initial diagnostic approach is a potentially simple, accurate, and cost-effective diagnosis strategy in patients with GERD (8, 30, 31, 59). It was found that over a period of 7 days, the symptom response rate of patients with NERD markedly improved from 27.2% to 83.3% when the omeprazole dose was increased from 40 mg once daily to 40 mg *b.i.d.* (59). This important study provides evidence that NERD patients also require a potent antireflux therapy for symptom control. Currently, there are no other studies using PPI therapeutic trials as a diagnostic tool in patients with NERD.

Upper endoscopy should be performed in all patients who present with alarm symptoms. The use of endoscopy as a screening tool for Barrett's esophagus remains controversial. Although recently, practice guidelines regarding Barrett's esophagus screening have been proposed by the American College of Gastroenterology, there is currently no consensus regarding at what point patients with GERD should be evaluated (60).

In patients undergoing upper endoscopy without esophageal mucosal injury, the addition of mucosal biopsy to detect histological changes consistent with GERD remains a common practice. The presence of inflammatory cells (neutrophils and eosinophils), epithelial hyperplasia (basal cell hyperplasia and elongated papillae), and dilated vessels in the papillae have all been considered to be markers of esophageal injury secondary to GERD in patients with intact-appearing mucosa (61). Using endoscopy and GERD symptoms as comparators, only 47.8% of NERD patients and 21.6% of normal controls had GERD-related histological findings in biopsies obtained 4 cm above the esophagogastric junction (62). In another study, histological findings typical of GERD were detected in 46% of NERD patients with abnormal pH testing, in 9% of those with normal pH tests, and in 29% of healthy controls (63). It seems from these studies that esophageal mucosal biopsies in NERD patients have a low yield and may not help to establish a diagnosis.

Diagnostic evaluation in NERD becomes increasingly important in patients who fail to respond to a standard dose of PPI. Failure of symptom control in NERD patients receiving PPI once a day (standard dose) is currently considered an indication for 24-h esophageal pH monitoring (64). However, when 57 NERD patients who continued to have symptoms of heartburn on a standard dose PPI underwent pH testing, the results were within the normal range in 61.1% (65). The extent of symptom control during therapy

with standard dose PPI seems to be related to the extent of intraesophageal acid exposure in the distal esophagus (51). The greater the total time that pH is initially  $<4$ , the better the symptom control. Thus, NERD patients with a mildly abnormal or normal pH test will often fail standard dose PPI treatment. This may be explained by either hypersensitivity to acid reflux in the physiological range, which may suggest the need for high dose PPI for complete acid elimination and consequent symptom control or by nonacid intraesophageal stimuli. A recent study demonstrated no increase in esophageal chemosensitivity to acid in NERD patients who failed standard dose PPI (31).

### QUALITY OF LIFE

A number of studies have demonstrated an impairment of quality of life in chronic erosive esophagitis. Tew *et al.* (66) studied the illness behavior of patients with NERD and found that these patients were similar to those with erosive esophagitis. Treatment improved both groups equally. In general, patients with GERD experience more pain and greater impairment in social functioning and emotional well-being than patients with other chronic diseases such as diabetes and hypertension. For example, Chal *et al.* found impairments in comfort (vs pain), vitality, and mental health in GERD (67). Dimenas reported impaired psychological well-being scores in patients with GERD (5). A small number of studies have evaluated patients with uninvestigated heartburn in primary care (68). Rust *et al.* demonstrated that impairment in quality of life was related to GERD symptoms and improved with therapy (ranitidine 150 mg *b.i.d.*) (69). Revicki *et al.* (70) studied 533 patients with a history of heartburn for 6 months before and after therapy with ranitidine, 150 mg *b.i.d.* Patients reported significantly worse scores on all eight scales of the SF-36 (physical function and well-being, emotional well-being) compared to the general population. Successful treatment led to marked improvement in the quality of life (70). Carlsson *et al.* (71) studied patients with endoscopy-negative reflux disease. The Psychological General Well-Being index (PGWB index) was used as a subjective measure of quality of life. Quality of life was impaired in patients with endoscopy negative disease and patients with erosive esophagitis and there were no significant differences between the groups. Omeprazole therapy improved the quality of life in both groups of patients (71). A recent study showed substantial improvement in quality of life with adequate therapy. Havellund *et al.* (72) studied quality of life using well validated scales in 163 patients with NERD. Quality of life was restored with omeprazole 10 mg or 20 mg and was comparable to that in the general population. Impairment of quality of life appears to be similar in patients with NERD and patients with erosive esophagitis. There is a strong association between symptoms and impairment of quality of life. Adequate treatment of symptoms therefore improves quality of life in patients with NERD.

### TREATMENT OF NERD

There are numerous therapeutic options available for treating patients presenting with symptoms of GERD or otherwise suspected as having this disease. Generally these therapeutic options have been viewed in a hierarchy of therapeutic efficacy, ranging from lifestyle modifications/antacids to histamine-2 receptor antagonists (H2RAs)/prokinetics to proton pump inhibitors (PPIs), with surgery reserved for those with continued symptoms or complications of GERD (73). It has been generally assumed by clinicians that patients with NERD would rarely demonstrate an incomplete response to either lifestyle modifications or therapy with H2RAs/prokinetics; thus, potent antisecretory therapy with PPIs or surgery should rarely be necessary in this patient population. However, there is now ample evidence that this assumption is incorrect, and that the therapeutic requirements of patients with NERD are similar to those with erosive esophagitis.

Some of the first evidence that H2RAs may be less than optimal as therapy for NERD came from a large US study of patients with heartburn treated with famotidine (74). In this trial,  $<30\%$  of patients treated with H2RA twice daily had complete elimination of heartburn at 30 days, and little more than 50% of patients had relief at the end of 3 months. A sizable number of patients in this trial had NERD or minimal grades of esophagitis. Thus, indirectly, evidence began to suggest that patients with NERD might not be as easily treated as previously assumed. This should not have been surprising, given the pharmacology of H2RAs. These agents have been known to be ineffective in inhibiting meal-stimulated acid secretion and are associated with the rapid development of pharmacological tolerance (73). These pharmacological properties affect all patients with GERD, regardless of the presence of erosive esophagitis. Further support for the inadequacy of these agents in many patients with NERD is derived from a recent trial in which symptomatic GERD patients with an incomplete response to therapy with 3 months of a twice daily dose of an H2RA, were randomized to a further 2 months of continued therapy at this dose or to 2 months of a double dose of the H2RA (75). Further therapeutic response to continued use of an H2RA, even at high doses, was very modest in this trial.

Given the pharmacological deficiencies of H2RAs in controlling acid secretion it was felt that perhaps patients with NERD could be better served by using a prokinetic agent. Prokinetics had shown some efficacy in patients with erosive esophagitis, and it was hoped even greater efficacy could be demonstrated in patients with NERD. However, in a large European study, remission of symptoms could be maintained in fewer than half of those patients with NERD who were receiving cisapride (76). Thus, like what had been observed for H2RAs, the therapeutic efficacy of prokinetics in patients with NERD is limited. Concerns about the safety of cisapride also limit its utility in this setting.

There are data that indicate overwhelmingly that, in pa-

tients with erosive esophagitis, PPIs provide superior healing and symptom relief compared to H2RAs or prokinetics (77). Similar data are emerging regarding the use of PPIs in patients with NERD. In a 4-wk study of patients with heartburn and normal endoscopy, omeprazole resulted in complete symptom relief in nearly 60% of patients *versus* approximately 20% of those receiving placebo (78). In a similar placebo-controlled trial, symptom relief at 4 wk was also approximately 60% in those receiving omeprazole *versus* 24% of those in the placebo arm (51). There were further interesting observations made in this study. The therapeutic response was correlated with intrasophageal acid exposure: those patients with the greatest intraesophageal acid exposure had the greatest response (response rate, >85% in patients with an esophageal pH of <4 more than 10% of the time, *vs* 54% in patients with a pH of <4 less than 4% of the time). Thus, in NERD patients with an abnormal pH study, the therapeutic response was nearly identical to that seen in patients with erosive esophagitis. The study also indicated that in those patients with functional heartburn, a therapeutic response would be much less likely.

There are now trials comparing the therapeutic efficacy of PPIs *versus* H2RAs and cisapride in patients with NERD. In one study, 60% of patients treated with omeprazole had relief of heartburn, *versus* 40% of those receiving H2RAs (79). In that study, >50% of patients were maintained in remission with omeprazole, *versus* <30% of those patients receiving ranitidine. Similarly, in a study in the US, lansoprazole has also been shown to be more effective than ranitidine in relieving symptoms of reflux in patients without esophagitis (80). Similar therapeutic superiority for PPIs has been shown in another trial comparing omeprazole to cisapride (81). In that study, 63% of omeprazole patients were free of heartburn at 4 wk, *versus* 46% of those receiving cisapride. These results that demonstrate superiority of omeprazole over placebo in patients with NERD have also been confirmed in recent US studies (82).

Although further studies are needed to clarify the efficacy of agents in NERD, certain conclusions can be made based on the evidence available in the literature. First, the therapeutic efficacy of antisecretory agents seems overall to be lower in patients with NERD compared to those with erosive esophagitis. Whether this is related to the inclusion of patients without GERD in these studies (thus diluting a treatment effect) or whether it is attributable to some other factor is unclear. Second, the hierarchy of efficacy of therapy (PPI efficacy is greater than that of H2RA/prokinetics, which is greater than lifestyle modifications alone) that is seen in patients with erosive esophagitis is comparable for patients with NERD. Third, patients with NERD demonstrate a similar lack of efficacy to H2RAs, as do those with erosive esophagitis. The results of surgery in patients with NERD have been thought by many clinicians to be poorer than the results obtained in patients with esophagitis. However there are few data to support this clinical impression. It is likely that patients selected for surgery based on complete

symptom response to antisecretory therapy will have symptom outcomes similar to those seen with esophagitis. NERD patients who do not respond to antisecretory therapy are unlikely to have an optimal response to antireflux surgery. Controlled trials of antireflux surgery are needed to determine the role of this therapy in patients with NERD.

## ECONOMICS OF ENDOSCOPY NEGATIVE REFLUX DISEASE

The costs of managing chronic disease are of increasing importance in an era of constrained resources. Determining the optimal therapy for patients with NERD is a growing area of interest and research.

### *Costs of Reflux Disease in the United States*

Acid-related disorders are common problems in the US, and GERD is the most prevalent of these disorders. Given the frequency of the condition, there are surprisingly few data on the total cost of managing reflux disease. In large measure, this is because information systems used in most institutions are not able to capture disease-specific costs throughout the entire episode of care. Levin *et al.* (83) reported the cost of managing reflux disease in a managed care organization in California (Kaiser Permanente of Northern California) and calculated the GERD-related costs in a cohort of 1500 patients with acid-related disorders. The total annual HMO expenditures for acid-related disorders was \$59 million for a membership of 2.4 million members. The total annual direct cost of managing a GERD patient was \$4574 with a total pharmacy cost of \$491, outpatient costs of \$2403 (pharmacy, outpatient visits, etc.), and inpatient costs of \$1680. With adjustment of the data to determine the costs attributable to GERD separately, the total cost of managing GERD was \$471 per person, with pharmacy costs accounting for \$156 of this amount and outpatient costs accounting for \$279; in comparison, inpatient costs were small at \$35/per person. In the first 6 months after the diagnosis, outpatient costs remain the highest component cost of GERD management, accounting for a large proportion of the adjusted costs (\$246 out of a total of \$289).

### *Outpatient Costs*

Outpatient costs of managing GERD are related to office visits and endoscopic or radiological procedures. GERD is one of the most frequent indications for upper endoscopy in the United States. In a large database of >17,000 endoscopic procedures, GERD was the third leading indication for endoscopy (84). With the understanding of the frequency of endoscopy-negative reflux disease, it has become appreciated that endoscopy may fail to establish a diagnosis of reflux disease, and alternative strategies have been proposed. Chief among these is a trial of therapy in primary care settings. Several studies have compared a short trial of acid inhibitory therapy as a diagnostic test for reflux disease to investigations such as a 24-h esophageal pH monitoring or endoscopy. They found that a trial of therapy may be an

effective method to diagnose patients with suspected reflux disease who present with symptoms of heartburn or chest pain. Ofman *et al.* reported the cost-effectiveness of the omeprazole test in patients with noncardiac chest pain (85). In patients with a cardiac cause excluded by comprehensive cardiac evaluation, the omeprazole test with no subsequent investigations for patients who respond, and with sequential testing with ambulatory 24-h esophageal pH monitoring, esophageal manometry, and endoscopy reserved for patients who do not respond, was the most effective and least expensive strategy. Using a selective strategy of investigation in nonresponders to a trial of a proton pump inhibitor, the authors calculated that a 43% reduction in procedures would result and that the cost-savings would be \$454 per patient compared with a strategy of beginning with endoscopy followed by pH testing and esophageal manometry. Similarly, in patients with suspected reflux disease, the omeprazole test was estimated to reduce the number of endoscopies performed by 64% and the number of pH studies by 53%, with \$348 saved per patient evaluated (86). Similarly in asthmatic patients, cost-effectiveness analysis suggests that a trial of therapy with omeprazole 20 mg/day for 3 months, with 24-h esophageal pH monitoring reserved for nonresponders, was cost-effective (87).

Sonnenberg *et al.* performed a decision analysis comparing empirical therapy versus diagnostic testing in GERD (88). Empirical therapy was cost saving, with investigation reserved for nonresponders, despite the cost associated with an occasional incorrect diagnosis. However, as the duration of therapy becomes longer (>10 yr in this particular model), investigation becomes more meaningful because maintenance therapy in patients who do not need therapy increases costs. Again, because of the relatively high cost of surgery, a specific diagnosis is favored in this subgroup of patients.

#### *Is Endoscopy Useful in Managing Therapy?*

Recent studies have examined the role of endoscopy in the management of patients with GERD. In a prospective study of 664 patients with symptoms of GERD who were undergoing upper endoscopy in clinical practice, 74% of patients who had Barrett's esophagus or erythema, erosions or ulceration at endoscopy had an increase in therapy after endoscopy (89). In contrast, 35% of patients who had a normal endoscopy had an increase in therapy. These data suggest that endoscopy may influence the treatment prescribed by physicians. However the increase in treatment in most cases was based on persistent symptoms or on findings in the stomach or duodenum. Blustein *et al.* evaluated the utility of endoscopy in a large group of 742 patients. In all, 68% of patients who were still symptomatic on H2Ras were switched to omeprazole regardless of the findings at endoscopy, whereas 47% of patients taking omeprazole were maintained on the same therapy regardless of the findings at endoscopy (90). Endoscopy therefore had a limited role in determining therapy.

#### *Relief of Anxiety With Endoscopy*

In dyspepsia, it has been suggested that endoscopy may relieve anxiety and reduce subsequent health care use (91). These data are based on uncontrolled studies of small groups of patients. Other studies have shown a short-term improvement in quality of life after endoscopy in dyspeptic patients (92). A recent study in a large cohort of patients suggested that patients with a high degree of anxiety before endoscopy continued to have high degrees of anxiety after a normal endoscopy and reassurance from the endoscopists. Patients with low levels of anxiety did not obtain significant benefit (93). A subgroup of patients with moderate anxiety did demonstrate lasting improvement of anxiety after a normal endoscopy. Endoscopy may therefore be useful in very selected patients for the relief of anxiety, and may be helpful in anxious patients with atypical symptoms of GERD, e.g., chest pain.

#### *Pharmacy Costs*

A number of economic models have examined the cost-effectiveness of treatment strategies for the management of erosive esophagitis, but there are few economic analyses on management strategies in endoscopy-negative reflux disease. Economic models that are directed at erosive esophagitis have limited applicability to unselected patients in primary care. Sonnenberg *et al.* examined a stepwise approach to the management of GERD in the VA system. They evaluated a stepwise strategy beginning with a generic H2RA; patients who failed to respond were treated with a higher dose of H2RA therapy, and those who still failed to respond were treated with proton pump inhibitors (step-up therapy) (94). This economic model suggested that an average of \$916 per patient could be saved every 5 yr by using a step-up strategy. In contrast, preliminary data from a clinical trial in primary care suggest that neither step-up or step-down therapy provided optimal control of heartburn over a 20-wk period (95). Recently a multicenter, randomized, open-label trial was performed in patients with symptoms of GERD in primary care practices in West Virginia. A total of 268 patients were randomized to received omeprazole 20 mg once a day or ranitidine (brand-name) 150 mg b.i.d. for up to 6 months. At 6 months, there was no significant difference in total costs between the groups, but symptoms were better controlled in the omeprazole group (96). These data suggest that effective therapies, which are more expensive to acquire, may still be cost-effective over relatively short periods of time because their higher efficacy decreases outpatient costs related to treatment failure.

As the natural history of endoscopy negative reflux disease is benign, control of symptoms is the principal determinant of the success of therapy. To reduce the cost of chronic maintenance therapy, alternate forms of maintenance therapy are being attempted in nonerosive reflux disease. New techniques of maintenance therapy offer significant advantages. These techniques consist of dose reduction or intermittent use of medication to reduce costs while

still achieving the goal of symptom relief. In a recent study, 677 patients with endoscopy-negative or mild-to-moderate erosive GERD in primary care were randomized to ranitidine 150 mg *b.i.d.*, low-dose omeprazole (10 mg/day), or standard dose omeprazole (20 mg/day) for 2 wk (97). If they had symptom relief they continued with the maintenance phase of the study, in which they received 2-wk courses of intermittent therapy with the regimen that had worked in the first instance. At the end of 1 yr of maintenance therapy, half of the patients did not require treatment for at least 6 months of the study period and had good control of symptoms, thus substantially reducing the cost of maintenance therapy. A cost analysis based on this study found no difference between the cost of the omeprazole and ranitidine arms, using cost assumptions from a number of European countries that were part of the trial. These data suggest that on a cost basis, there is little to be gained from a step-up approach to treating NERD (98).

Another alternative is to give on-demand therapy, thereby reducing the amount of medication being used. In one study, 424 patients with endoscopy negative reflux disease were randomized to placebo or PPI (omeprazole 20 mg or omeprazole 10 mg) on demand (99). At 6 months follow-up, 29% of patients had failed to respond to on-demand therapy and needed daily maintenance therapy. However 83% of patients randomized to on-demand therapy with omeprazole 20 mg a day were satisfactorily maintained over the 6-month time frame. The mean number of omeprazole capsules used per day was 0.43, suggesting that the total medication use was reduced by approximately 50%. In the future, patients with NERD will increasingly be managed with alternative forms of maintenance therapy. Some conclusions regarding the economics of NERD can be made from the available data. First, the cost of managing all forms of reflux disease is high. Second, outpatient costs are the major component of the management costs of NERD. Third, endoscopy—although useful for diagnosis—has little role in management, which is driven by symptoms. Fourth, new methods of PPI administration may be an interesting new option in the management of NERD, combining highly effective therapy with less frequent administration, thereby reducing cost.

In conclusion, NERD is a common condition in primary care. Many patients with NERD have moderate-to-severe symptoms and significant impairment in the quality of life. Therapy with acid-suppressive agents results in complete resolution of symptoms in the majority of patients and restores quality of life. Current data from surgical studies are inadequate to determine whether surgical therapy results in better or worse outcomes than medical therapy. Alternative methods of treatment including on-demand therapy and intermittent therapy deserve further study and may help to reduce the costs of maintenance therapy.

Center, 945 North 12th Street, Room 4040, Milwaukee, WI 53233-1305.

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# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY

## Control of Gastric Acid Secretion in Health and Disease

MITCHELL L. SCHUBERT\* and DAVID A. PEURA†

\*Department of Medicine, Division of Gastroenterology, Virginia Commonwealth University's Medical College of Virginia, McGuire Veterans Affairs Medical Center, Richmond, Virginia; and †Department of Medicine, Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, Virginia

Recent milestones in the understanding of gastric acid secretion and treatment of acid-peptic disorders include the (1) discovery of histamine  $H_2$ -receptors and development of histamine  $H_2$ -receptor antagonists, (2) identification of  $H^+K^+$ -ATPase as the parietal cell proton pump and development of proton pump inhibitors, and (3) identification of *Helicobacter pylori* as the major cause of duodenal ulcer and development of effective eradication regimens. This review emphasizes the importance and relevance of gastric acid secretion and its regulation in health and disease. We review the physiology and pathophysiology of acid secretion as well as evidence regarding its inhibition in the management of acid-related clinical conditions.

Is the study of gastric acid now only of historical interest? Many have forgotten the central role acid played in shaping gastroenterology as a specialty. It was in the acid era that our specialty was defined and flourished. Acid was meticulously measured in an attempt to better understand and treat peptic ulcer disease, the major clinical challenge at that time. Fiberoptic endoscopy was developed to better define upper gastrointestinal acid-related mucosal damage. Acid neutralization consumed clinicians. Antacids were dispensed, not by the bottle, but by the case. Neutralizing capacity, taste, sodium content, and adverse effect profile (diarrhea or constipation) of the various antacids were hot issues debated at national meetings because, to adequately control acid, antacids were dosed 1 and 3 hours after meals and at bedtime.<sup>1</sup> Anticholinergic medications, despite their associated adverse effects, were prescribed before meals and at bedtime to prolong gastric emptying of antacids and to control nocturnal ulcer symptoms.<sup>2</sup> Gastric freezing and radiation were modalities employed to reduce acid in patients with "medically refractory" symptoms when surgery was not a consideration.<sup>3</sup> Peptic ulcer surgery was planned based on gastric acid output measurement: high acid secretion generally indicated a more extensive resection. Too much postoperative acid (incom-

plete vagotomy) meant ulcer recurrence, whereas too little acid (large resection) had nutritional consequences.<sup>4,5</sup> Milk alkali syndrome, gastric outlet obstruction, and dumping syndrome, complications largely unknown to today's gastroenterology fellows, were common occurrences.<sup>6</sup> All this characterized the "BC" (before cimetidine) era of gastroenterology.

Sir James Black's Nobel Prize winning discovery of  $H_2$ -receptor antagonists ( $H_2$ RAs) in 1972 shed new light on acid secretion and changed the practice of gastroenterology forever.<sup>7</sup> For the first time, acid could be inhibited and ulcers predictably healed. Studies showed that the duration and degree of acid inhibition (percentage of the day pH >3) determined ulcer healing, and once daily dosing of  $H_2$ RAs at bedtime was the most efficient healing regimen.<sup>8,9</sup> In addition, continuous bedtime administration of the medication could prevent ulcer recurrence, the first step in controlling this chronic condition.

More recently, the identification of hydrogen-potassium-stimulated adenosine triphosphatase ( $H^+K^+$ -ATPase) as the proton pump of the parietal cell and *Helicobacter pylori* (HP) infection as the main cause of gastric and duodenal ulcer (also Nobel Prize winning) heralded a new revolution in our understanding and treatment of acid-peptic disorders.<sup>10-14</sup> Dosed before mealtime, proton pump inhibitors (PPIs) are the most effective acid inhibitors currently available and are the most widely prescribed class of gastrointestinal medications. Not only can peptic ulcers be healed more rapidly with PPIs, but refractory ulcers have all but disappeared. Eradication of HP with antibiotics, offered, for the first time, a permanent cure for most ulcers.

**Abbreviations used in this paper:** CGRP, calcitonin gene-related peptide; GERD, gastroesophageal reflux disease; GRP, gastrin-releasing peptide;  $H_2$ RAs,  $H_2$ -receptor antagonists; HP, *Helicobacter pylori*; MEN-1, multiple endocrine neoplasia type 1; NSAID, nonsteroidal antiinflammatory drug; PACAP, pituitary adenylate cyclase-activating polypeptide; PPIs, proton pump inhibitors; VIP, vasoactive intestinal polypeptide; ZES, Zollinger-Ellison syndrome.

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As the prevalence of HP infection has declined, because of improved sanitation and efforts to eradicate the organism, the prevalence of nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers and HP-negative/NSAID-negative ulcers has risen and is taking on greater clinical importance. Schwarz's dictum "no acid, no ulcer" remains valid, even today.<sup>15</sup> Acid control remains the mainstay for the treatment and prevention of ulcers caused by NSAIDs, gastrinoma (Zollinger-Ellison syndrome [ZES]), and stress as well as HP-negative/NSAID-negative idiopathic ulcers.<sup>16,17</sup>

The era of effective management of ulcers has ushered in a new acid-related challenge, gastroesophageal reflux disease (GERD). Until recently, the clinical importance of reflux had been largely underappreciated because peptic ulcers were so prominent. As with ulcers, the duration and degree of acid inhibition were shown to correlate with healing of erosive esophagitis and control of reflux symptoms.<sup>18</sup> However, a greater degree and duration of 24-hour acid inhibition were required to effectively manage GERD than H2RAs could provide. Although H2RAs could improve the condition, they could not predictably heal esophagitis (especially severe grades) or eliminate symptoms. It was this clinical niche for which the PPIs were ideally suited. PPIs can predictably heal esophagitis, no matter how severe, and prevent recurrence.<sup>19,20</sup> Although currently available PPIs can eliminate most reflux symptoms, better therapies are needed to eliminate nighttime reflux, symptoms in patients with endoscopic-negative reflux disease, and alleged extraesophageal manifestations of GERD such as cough and asthma.<sup>21-23</sup>

The purpose of this review is to reemphasize the importance and relevance of gastric acid secretion and its

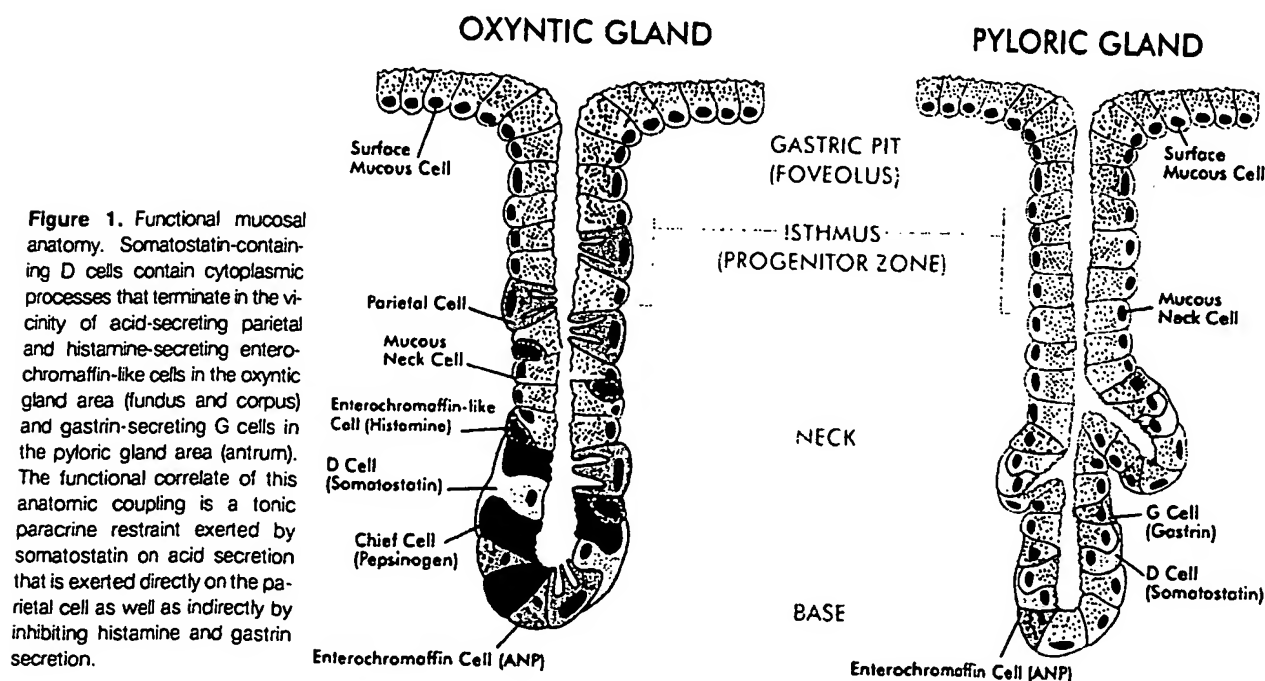
regulation. We will review the physiology and pathophysiology of acid secretion as well as evidence regarding its inhibition in the management of acid-related clinical conditions. As we reexamine and update this area, we hope to rekindle the excitement surrounding acid that was at the roots of gastroenterology and provide information relevant to the future care of patients with acid-peptic disorders.

## Functional Anatomy of the Stomach

### Mucosal Anatomy

The stomach consists of 3 topographic (fundus, corpus, and antrum) and 2 functional (oxyntic and pyloric gland) areas. The oxyntic gland area, the hallmark of which is the oxyntic (oxy, Greek for acid) or parietal cell, comprises 80% of the organ (fundus and corpus). The pyloric gland area, the hallmark of which is the gastrin or G cell, comprises 20% of the organ (antrum). It is estimated that the human stomach contains  $1 \times 10^9$  parietal and  $9 \times 10^6$  gastrin cells.<sup>24</sup> There is debate as to whether the cardia, a transition zone of 0-9 mm between the squamous mucosa of the esophagus and the oxyntic mucosa of the stomach, exists as a normal anatomic structure or develops as a result of abnormal reflux. Autopsy and endoscopic studies suggest that cardiac mucosa is absent in over 50% of the general population.<sup>25</sup>

The oxyntic gland area is organized in vertical tubular units that consist of an apical pit region, an isthmus, and the actual gland region that forms the lower part of the unit (Figure 1). The gland consists of a neck and a base. The progenitor cell of the gastric unit, located in the isthmus, gives rise to all gastric epithelial cells. The mu-



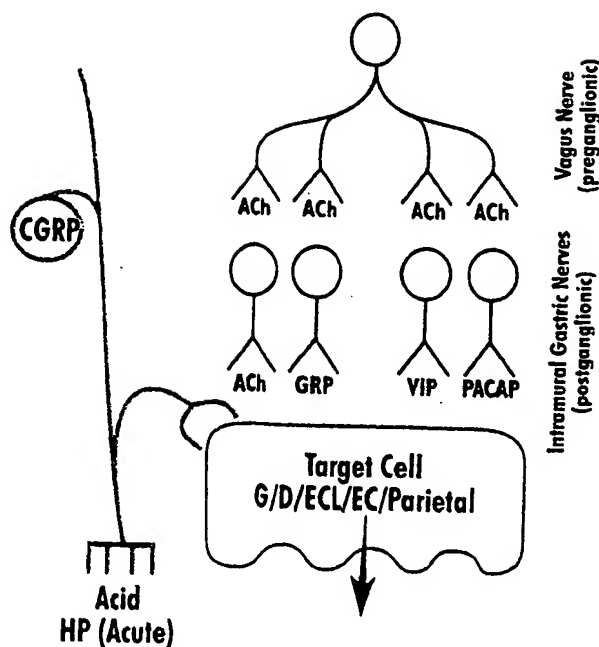
**Figure 1.** Functional mucosal anatomy. Somatostatin-containing D cells contain cytoplasmic processes that terminate in the vicinity of acid-secreting parietal and histamine-secreting enterochromaffin-like cells in the oxyntic gland area (fundus and corpus) and gastrin-secreting G cells in the pyloric gland area (antrum). The functional correlate of this anatomic coupling is a tonic paracrine restraint exerted by somatostatin on acid secretion that is exerted directly on the parietal cell as well as indirectly by inhibiting histamine and gastrin secretion.

cus-producing pit cells migrate upward from the progenitor cell toward the gastric lumen. Acid-secreting parietal cells migrate downward to the middle and lower regions of the gland. As parietal cells descend to the deeper regions, they become less active acid producers.<sup>26</sup> The turnover time for parietal cells is 54 days in mouse and 164 days in rat.<sup>24</sup> In rat and human, zymogenic (chief) cells predominate at the base of the glands and secrete pepsinogen and leptin<sup>27</sup>; the latter is also present in parietal cells.<sup>28</sup> Neuroendocrine cells containing a host of potential hormonal and paracrine signaling agents are contained within the gland, only some of which have been assigned physiologic functions: (1) enterochromaffin (EC) cells contain atrial natriuretic peptide (ANP), serotonin, and adrenomedullin<sup>29,30</sup>; (2) enterochromaffin-like (ECL) cells contain histamine<sup>31,32</sup>; (3) D cells contain somatostatin and amylin<sup>33,34</sup>; and (4) A-like or Gr cells contain ghrelin and obestatin.<sup>35,36</sup> Neuroendocrine cells comprise 2% of epithelial cells in rat and 1% in human.<sup>32</sup> ECL cells constitute 66% of the neuroendocrine cell population in rat and 30% in human. Somatostatin-containing D cells possess cytoplasmic processes that terminate in the vicinity of parietal and ECL cells. The functional correlate of this anatomic coupling in rat, dog, and human oxyntic mucosa is a tonic paracrine restraint exerted by somatostatin on acid secretion directly as well as indirectly by inhibiting histamine secretion<sup>37-39</sup> (Figure 1).

Somatostatin-containing D cells are also present in the pyloric gland area; in this region, they exert a tonic paracrine restraint on gastrin secretion from G cells<sup>40,41</sup> (Figure 1). The pyloric gland also contains EC cells (ANP and serotonin), A-like or Gr cells (ghrelin and obestatin), and endocrine cells containing orexin.<sup>30,42,43</sup>

### Neural Anatomy

The stomach is innervated by a neural network, the enteric nervous system (ENS), that contains intrinsic neurons and processes of extrinsic efferent and afferent neurons. The ENS, the third division of the autonomic nervous system (the other 2 being the sympathetic and parasympathetic), is often referred to as the "little brain" because it contains as many neurons as the spinal cord, ~10<sup>8</sup>, and can function autonomous of central input.<sup>44</sup> In rat and guinea pig, most of the intrinsic neural innervation of the stomach originates in the myenteric plexus, located between the circular and longitudinal muscle layers; the submucosal plexus, adjacent to the mucosal layer, contains only a small number of neurons. Humans, in contrast, have a clearly defined submucosal plexus. It should be noted that the vagus nerve contains 80%-90% afferent fibers and only 10%-20% efferent fibers. The efferent fibers are preganglionic and do not directly innervate parietal or neuroendocrine cells but rather synapse with postganglionic neurons of the ENS (Figure 2). The postganglionic neurons contain a variety of transmitters includ-

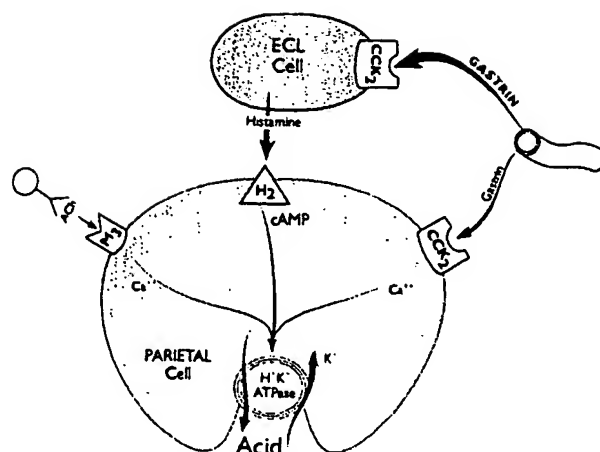


**Figure 2.** Functional neural anatomy. The vagus contains preganglionic neurons that synapse with postganglionic neurons within the wall of the stomach that are part of the enteric nervous system. The postganglionic neurons contain a variety of transmitters including acetylcholine (ACh), gastrin-releasing peptide (GRP or mammalian bombesin), vasoactive intestinal polypeptide (VIP), and pituitary adenylate cyclase activating polypeptide (PACAP). In the stomach, calcitonin gene-related peptide (CGRP) neurons are sensory and of extrinsic origin; they can be activated by luminal acid and acute infection with *Helicobacter pylori* (HP). The postganglionic neurons regulate acid secretion directly and/or indirectly by modulating the secretion of gastrin from G cells, somatostatin from D cells, histamine from enterochromaffin-like (ECL) cells, and atrial natriuretic peptide from enterochromaffin (EC) cells.

ing acetylcholine (ACh), gastrin-releasing peptide (GRP), vasoactive intestinal polypeptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), nitric oxide, and substance P.<sup>45</sup> In rat and human stomach, nerve fibers containing calcitonin gene-related peptide (CGRP) are of extrinsic origin, ie, the cell bodies are located outside the stomach wall.<sup>46</sup> Postganglionic neurons of the ENS regulate acid secretion directly, as is the case for ACh, and/or indirectly by modulating the secretion of gastrin from G cells, somatostatin from D cells, histamine from ECL cells, and ANP from EC cells (Figure 2).

### Gastric Acid Secretion: Neural, Hormonal, Paracrine, and Intracellular Regulation

Parietal cells secrete hydrochloric acid at a concentration of approximately 160 mmol/L or pH 0.8. Acid is thought to gain access to the lumen via channels in the mucus layer created by the relatively high intraglandular hydrostatic pressures generated during secretion, approximately 17 mm Hg.<sup>47</sup> Most studies indicate that the rate of acid secretion by the human stomach changes little with



**Figure 3.** Model illustrating parietal cell receptors and transduction pathways. The principal stimulants of acid secretion at the level of the parietal cell are histamine (paracrine), gastrin (hormonal), and acetylcholine (ACh; neurocrine). Histamine, released from enterochromaffin-like (ECL) cells, binds to  $H_2$  receptors that activate adenylate cyclase (AC) and generate cAMP. Gastrin, released from G cells, binds to  $CCK_2$  receptors that activate phospholipase C to induce release of cytosolic calcium ( $Ca^{2+}$ ). Gastrin stimulates the parietal cell directly and, more importantly, indirectly by releasing histamine from ECL cells. ACh, released from intramural neurons, bind to  $M_3$  receptors that are coupled to an increase in intracellular calcium. The intracellular cAMP- and calcium-dependent signaling systems activate downstream protein kinases ultimately leading to fusion and activation of  $H^+K^+$ -ATPase, the proton pump.

aging unless there is coexisting disease of the oxyntic mucosa such as infection with HP or atrophic gastritis.<sup>48,49</sup>

Acid facilitates the digestion of protein and absorption of iron, calcium, and vitamin B-12 as well as prevents bacterial overgrowth and enteric infection.<sup>50</sup> However, when levels of acid (and pepsin) overwhelm mucosal defense mechanisms, ulcers occur. To prevent such damage, gastric acid must be precisely regulated. This is accomplished by a highly coordinated interaction of neural, hormonal, and paracrine pathways. These pathways can be activated directly by stimuli originating in the brain or reflexively by stimuli originating in the stomach such as distension, protein, and acid.

The principal stimulants of acid secretion are (1) histamine, released from ECL cells (paracrine); (2) gastrin, released from G cells (hormonal); and (3) ACh, released from postganglionic enteric neurons (neurocrine) (Figure 3). These agents interact with receptors coupled to 2 major signal transduction pathways: adenylate cyclase in the case of histamine and intracellular calcium in the case of gastrin and ACh (Figure 3). In isolated dog and rabbit parietal cells, there is evidence for potentiation (or synergism) between histamine and either ACh or gastrin, probably as a result of postreceptor interaction between the 2 signaling pathways.<sup>51</sup> The main inhibitor of acid secretion is somatostatin, released from oxyntic and pyloric D cells (paracrine). Each of these agents acts directly

on the parietal cell as well as indirectly by modulating the secretion of neuroendocrine cells.

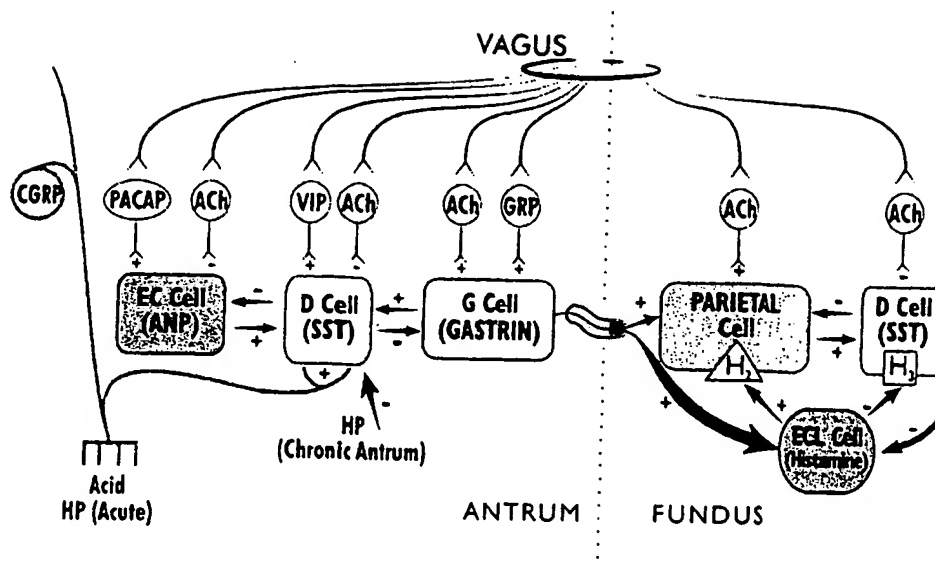
### Histamine

Histamine, produced in ECL cells by decarboxylation of L-histidine by histidine decarboxylase (HDC), stimulates the parietal cell directly by binding to  $H_2$  receptors coupled to activation of adenylate cyclase and generation of adenosine 3',5'-cyclic monophosphate (cAMP).<sup>52</sup> Histamine also stimulates acid secretion indirectly by binding to  $H_3$  receptors coupled to inhibition of somatostatin and thus stimulation of histamine and acid secretion.<sup>53,54</sup> (Figure 4). Gastrin, PACAP, VIP, and ghrelin stimulate, whereas somatostatin, CGRP, prostaglandins, peptide YY (PYY), and galanin inhibit histamine secretion.<sup>55,56</sup> ACh has no direct effect on histamine secretion.<sup>57-59</sup>

### Gastrin

Gastrin, the main stimulant of acid secretion during meal ingestion, is produced in G cells of the gastric antrum and, in much lower and variable amounts, in the proximal small intestine, colon, and pancreas. Gastrin is synthesized as a large precursor molecule of 101 amino acids, which is processed to yield the glycine-extended peptides G34gly and G17gly, which, in turn, are amidated to yield G34amide and G17amide. In human antrum, the concentration of amidated gastrin is approximately 5-fold greater than that of glycine-extended gastrin, whereas in the circulation there are approximately equal concentrations of amidated and glycine-extended gastrins.<sup>60,61</sup> The half-life of G17 in the plasma of pigs is approximately 3.5 minutes; it is metabolized primarily by the kidney and, in addition, the intestine and liver.<sup>62,63</sup> In patients with renal insufficiency, fasting blood levels of G17, G34, and Gly-gastrin are elevated.<sup>64,65</sup> It should be noted that the commercially available test substance pentagastrin (Peptavlon) is not a naturally occurring peptide but rather is a manufactured analogue that contains the biologically active C-terminus sequence Trp-Met-Asp-Phe-NH<sub>2</sub>.

Gastrin and cholecystokinin (CCK) possess an identical carboxyl-terminal pentapeptide sequence (-Gly-Trp-Met-Asp-Phe-NH<sub>2</sub>). Two main classes of gastrin/CCK receptors have been characterized:  $CCK_1$  (formerly  $CCK-A$ ) and  $CCK_2$  (formerly  $CCK_B$  or  $CCK_B$ /gastrin).  $CCK_1$  receptors are specific for CCK, whereas  $CCK_2$  receptors recognize both CCK and gastrin with high affinity.  $CCK_2$  receptors have been identified on human parietal and ECL cells where they are coupled to activation of phospholipase C and release of intracellular calcium.<sup>66-68</sup> There is debate as to whether activation of the parietal cell  $CCK_2$  receptor leads to acid secretion.<sup>69,70</sup> It seems that intracellular concentrations of cAMP must first be above a threshold before gastrin can directly stimulate the parietal cell.<sup>51,71</sup> It is thought that the primary action



**Figure 4.** Model illustrating the neural, paracrine, and hormonal regulation of gastric acid secretion. Efferent vagal fibers synapse with intramural gastric cholinergic (ACh) and peptidergic (gastrin-releasing peptide [GRP], vasoactive intestinal peptide [VIP], and pituitary adenylate-cyclase activating peptide [PACAP]) neurons. In the fundus (oxyntic mucosa), ACh neurons stimulate acid secretion directly via  $M_3$  receptors on the parietal cell and indirectly by inhibiting somatostatin (SST) secretion, thus eliminating its restraint on parietal cells and histamine-containing enterochromaffin-like (ECL) cells. In the antrum (pyloric mucosa), ACh neurons stimulate gastrin secretion directly and indirectly by inhibiting SST secretion, the latter by a direct effect on the D cell and an indirect effect mediated by inhibition of atrial natriuretic peptide (ANP) secretion from enterochromaffin (EC) cells. GRP neurons, activated by intraluminal protein, also stimulate gastrin secretion. VIP neurons, activated by low-grade distension, stimulate SST and thus inhibit gastrin secretion. PACAP neurons stimulate SST, via release of ANP, and thus also inhibit gastrin secretion. Dual paracrine pathways link SST-containing D cells to parietal cells and to ECL cells. Histamine released from ECL cells acts via  $H_2$  receptors to inhibit SST secretion. This serves to accentuate the decrease in SST secretion induced by cholinergic stimuli and thus augments acid secretion. In the antrum, dual paracrine pathways link SST-containing D cells to gastrin cells and to EC cells. Release of acid into the lumen of the stomach restores SST secretion in both the fundus and antrum; the latter is mediated via release of calcitonin gene-related peptide (CGRP) from extrinsic sensory neurons. Acute infection with HP also activates CGRP neurons to stimulate SST and thus inhibit gastrin secretion. In duodenal ulcer patients chronically infected with HP, the organism or cytokines released from the inflammatory infiltrate inhibit SST and thus stimulate gastrin (and acid) secretion.

of gastrin on the parietal cell may be to sensitize it to other secretagogues through cross talk/synergistic interaction between the signaling pathways. Activation of the  $CCK_2$  receptor on the ECL cell with release of histamine is presently thought to be the main pathway by which gastrin stimulates acid secretion (Figures 3 and 4).<sup>67,68</sup> Gastrin regulates the secretion and synthesis of histamine in a biphasic manner. The first phase involves release of stored histamine. The second phase relates to the replenishment of histamine stores and involves an increase in HDC activity followed by an increase in HDC gene transcription.<sup>72</sup>  $H_2$  receptor, HDC, and  $CCK_2$  receptor knockout mice manifest decreased acid secretion, especially in response to gastrin.<sup>73-75</sup>

ACh, GRP, secretin,  $\beta_2/\beta_3$ -adrenergic agonists, calcium, aromatic amino acids, and alcoholic beverages produced by fermentation stimulate, whereas somatostatin, galanin, and adenosine inhibit gastrin secretion. In addition, at least 2 negative feedback pathways, mediated via release of somatostatin, regulate gastrin secretion. The first is activated by luminal acidity and, in rats, involves sensory CGRP neurons (Figure 4). Low intragastric pH (high intragastric acidity) activates CGRP neurons that, via an axon reflex, stimulate somatostatin and thus in-

hibit gastrin secretion.<sup>76-78</sup> Conversely, when intragastric pH rises (low intragastric acidity), for example, by anti-secretory medications such as PPIs or gastric atrophy, somatostatin secretion is inhibited, and patients develop hypergastrinemia. There is some evidence, in mouse, that bacterial overgrowth induced by hypochlorhydria may also contribute to hypergastrinemia.<sup>79</sup> The second negative feedback pathway involves a paracrine pathway whereby gastrin directly stimulates somatostatin and thus attenuates its own secretion (Figure 4).<sup>80</sup>

Gastrin is also a trophic hormone.  $CCK_2$  receptors have been localized to the progenitor zone in oxyntic glands, and chronic hypergastrinemia induces proliferation of ECL and parietal cells directly as well as indirectly via the autocrine or paracrine action of growth factors such as heparin-binding epidermal growth factor, amphiregulin, transforming growth factor- $\alpha$ , metalloproteinases, and regenerating islet-derived 1.<sup>81,82</sup> Rats rendered hypergastrinemic with a PPI demonstrate a 5-fold increase in the number of ECL cells and a 1.5-fold increase in the number of parietal cells.<sup>83</sup> Gastrin acts directly on ECL cells to induce hyperplasia, dysplasia, and eventually neoplasia (carcinoids).<sup>84</sup> In contrast to rodents, humans rarely develop carcinoid tumors in response to hypergastrinemia

unless other factors are present such as chronic atrophic gastritis or gastrinoma associated with multiple endocrine neoplasia type 1 (MEN-1).<sup>85</sup> In the latter, carcinoids occur in 13% to 43%. Because ECL cells contain somatostatin subtype 2 receptors, somatostatin scintigraphy with [<sup>111</sup>In-DTPA]octreotide is the preferred imaging method to detect carcinoid tumors with an overall sensitivity of 80% to 100%.<sup>86,87</sup>

### ACh

Muscarinic receptors on parietal cells are of the M<sub>3</sub> subtype. Like CCK<sub>2</sub> receptors, M<sub>3</sub> receptors are coupled to activation of phospholipase C with generation of inositol trisphosphate and release of intracellular calcium<sup>88</sup> (Figure 3). Alcoholic beverages produced by fermentation stimulate gastric acid secretion, and the effect may be mediated via activation of M<sub>3</sub> receptors.<sup>89</sup> ACh also stimulates acid secretion indirectly by activating M<sub>2</sub> and M<sub>4</sub> receptors on D cells coupled to inhibition of somatostatin secretion, thus removing the tonic restraint exerted by this peptide on gastrin, ECL, and parietal cells (Figure 4).

### Somatostatin

The main inhibitor of acid secretion is somatostatin. Somatostatin is synthesized from a 92-amino acid preprosomatostatin precursor molecule that is processed to yield somatostatin-14 and somatostatin-28. Somatostatin-14 is predominantly found in stomach, pancreatic islets, and enteric neurons, whereas somatostatin-28 is the major form in the small intestine.

In stomach, somatostatin cells are closely coupled to their target cells (eg, parietal, ECL, and gastrin cells) either directly via cytoplasmic processes or indirectly via the local circulation.<sup>34,90</sup> In rat, dog, and human, the functional correlate of this anatomic coupling is a tonic restraint exerted by somatostatin on acid secretion from the parietal cell, histamine secretion from the ECL cell, and gastrin secretion from the G cell.<sup>37,38,41,91,92</sup> Removing this restraint (ie, disinhibition or elimination of the influence of an inhibitor), by activation of cholinergic neurons, is an important physiologic mechanism for stimulating acid secretion. In the stomach, the actions of somatostatin are thought to be mediated via the somatostatin subtype 2 receptor.<sup>93-95</sup> Gastrin, GRP, VIP, PACAP,  $\beta$ 2/ $\beta$ 3-adrenergic agonists, secretin, ANP, adrenomedullin, amylin, adenosine, and CGRP stimulate, whereas ACh and interferon- $\gamma$  inhibit somatostatin secretion. As mentioned above, an increase in luminal acidity acts to attenuate acid secretion via a pathway involving release of somatostatin in both antrum and fundus. In mouse, the change in somatostatin secretion is encompassed by luminal acidity in the range of pH 3 to pH 5, which is within the range observed after ingestion of a meal.<sup>96</sup>

### Miscellaneous Substances

Most studies report that ghrelin stimulates acid secretion, although one study reported no effect on basal secretion and a decrease in pentagastrin-stimulated acid secretion in awake rats equipped with a gastric fistula.<sup>97,98</sup> The stimulatory effect of ghrelin appears to involve the vagus nerve and histamine release because the stimulatory effect is abolished by vagotomy and is associated with an increase in HDC messenger RNA.<sup>99,100</sup>

ANP, CCK, secretin, glucagon-like peptide, peptide YY, adrenomedullin, amylin, neurotensin, glucose-dependent insulintropic polypeptide, leptin, and epidermal growth factor stimulate somatostatin and thus inhibit acid secretion.<sup>29,30,33,101</sup> CCK may function as a physiologic enterogastrone, ie, an intestinal factor responsible for the inhibition of acid secretion induced by the presence of nutrients in the intestine.<sup>102,103</sup> Interleukin-1 $\beta$  and serotonin inhibit acid secretion.<sup>104,105</sup>

### H<sup>+</sup>K<sup>+</sup>-ATPase

Parietal cell secretion is increased by activation of intracellular cAMP- and calcium-dependent signaling pathways that activate downstream protein kinases, ultimately leading to fusion and activation of H<sup>+</sup>K<sup>+</sup>-ATPase, the proton pump (Figure 3). This enzyme, which consists of 2 subunits, catalyzes the electroneutral exchange of luminal K<sup>+</sup> for cytoplasmic H<sup>+</sup>. The  $\alpha$ -subunit carries out the catalytic and transport functions of the enzyme and also contains sequences responsible for apical membrane localization.<sup>106</sup> The  $\beta$ -subunit, which is heavily glycosylated, protects the enzyme from degradation and is necessary for trafficking to and from the plasma membrane.<sup>107</sup>

In the resting unstimulated state, H<sup>+</sup>K<sup>+</sup>-ATPase activity is contained predominantly within cytoplasmic tubulovesicles. Upon stimulation, these vesicles fuse with the apical plasma membrane, resulting in extensive infoldings. Upon cessation of secretion, the H<sup>+</sup>K<sup>+</sup>-ATPase is retrieved from the apical membrane, and the tubulovesicular compartment is reestablished. The precise mechanism regulating trafficking are not known, but data suggest that it involves actin-based microfilaments, small GTPases, docking/fusion proteins, cytoskeletal linkers, and clathrin.<sup>108-110</sup>

Current PPIs (eg, omeprazole) consist of 2 heterocyclic moieties, a pyridine and a benzimidazole ring, connected by a methylsulfinyl group. They are weak bases (pK<sub>a</sub> 4–5) that are membrane permeable in the nonprotonated form and relatively impermeable in the protonated form. As a result, they accumulate in acidic spaces with a pH <4. The pK<sub>a</sub> of a molecule, which is based on a logarithmic scale, refers to the degree of willingness of the compound to accept or donate a proton. When a compound is in an environment with a pH equal to its pK<sub>a</sub>, half the molecules will be protonated, and half will be nonprotonated. In blood (pH 7.4), PPIs are essentially nonprotonated.

nated and thus pass readily into and through cells (time to reach peak plasma concentration, ~2 hours; elimination half-life, ~1 hour). However, when they enter the secretory canaliculus of the parietal cell ( $\text{pH} < 1$ ), >99.9% of the PPI becomes protonated and trapped.<sup>111</sup> PPIs then undergo an acid-catalyzed chemical rearrangement, probably to a sulfenamide or sulfenic acid, that permits them to inhibit  $\text{H}^+\text{K}^+\text{-ATPase}$  by forming covalent disulfide bonds with cysteine residues on the lumenally exposed  $\alpha$ -subunit of the  $\text{H}^+\text{K}^+\text{-ATPase}$ .<sup>112</sup> Whereas all PPIs bind to cysteine 813, omeprazole also binds to cysteine 892, lansoprazole to cysteine 321, and pantoprazole to cysteine 822. Because only the inserted  $\text{H}^+\text{K}^+\text{-ATPase}$  is susceptible to blockade by PPIs and an acid environment ( $\text{pH} < 4$ ) is necessary for both trapping and activating the PPI, the potency of PPIs is decreased when they are administered during the basal state or when acid secretion is inhibited.<sup>113,114</sup> Because most pumps are inserted with breakfast, it is recommended that PPIs be taken a half hour to 1 hour before the first meal. If greater inhibition is needed, an additional dose should be taken before dinner. Seventy percent of primary care physicians and 20% of gastroenterologists prescribe PPIs suboptimally, either at bedtime or unrelated to food intake; this is the most common cause of PPI failure.<sup>115</sup>

Autoimmune gastritis is an inflammatory disorder of the oxyntic mucosa often associated with antiparietal cell autoantibodies directed against  $\text{H}^+\text{K}^+\text{-ATPase}$  with subsequent loss of parietal cells.<sup>116</sup>  $\text{H}^+\text{K}^+\text{-ATPase}$  is a major autoantigen in a subset of patients infected with HP, and these antibodies may play a role in the subsequent development of atrophic gastritis. It is postulated that antibodies are acquired due to molecular mimicry between HP lipopolysaccharide and  $\text{H}^+\text{K}^+\text{-ATPase}$ , both of which contain Lewis epitopes.<sup>117</sup> Interestingly, a proportion of patients with duodenal ulcer, approximately 20%, also have antiparietal cell antibodies. These patients have more severe body gastritis, higher gastrin levels, and decreased peak acid outputs compared with patients with duodenal ulcer without antibodies.<sup>118</sup>

### Apical Channels

Proton secretion occurs in the parietal cell by exchanging  $\text{H}^+$  for  $\text{K}^+$  via the  $\text{H}^+\text{K}^+\text{-ATPase}$ . This is coupled with extrusion of  $\text{Cl}^-$  via an apical chloride channel and  $\text{K}^+$  via an apical potassium channel. Parietal cell proton secretion is impaired by (1) knockout of KCNE2, a gene that encodes single transmembrane domain subunits that regulate the function of voltage gated potassium channels,<sup>119</sup> and (2) inhibition of cystic fibrosis transmembrane conductance regulator, a cAMP-regulated chloride channel present in parietal cells.<sup>120</sup> These channels may provide targets for the development of novel antisecretory drugs. For example, AZD0865 (8-[2,6-dimethylbenzyl]amino]-N-(2-hydroxyethyl)-2,3-dimethylimidazo[1,2- $\alpha$ ]pyridine-(6-carboxamide), a drug that in-

hibits  $\text{H}^+\text{K}^+\text{-ATPase}$  by potassium-competitive binding at or near the potassium binding site of the enzyme, may have a more rapid onset and longer duration of effect than PPIs and effectively heals esophagitis.<sup>121</sup>

### Integrated Response to a Meal: Interplay of Neural, Paracrine, and Hormonal Mechanisms

Stimuli originating inside and outside the stomach converge on gastric efferent neurons that are the primary regulators of acid secretion. The effector neurons comprise cholinergic neurons and 3 types of noncholinergic neurons: GRP, VIP, and PACAP neurons. The neurons act on target cells directly as well as indirectly by regulating release of gastrin, histamine, somatostatin, and ANP (Figures 2 and 4).

During the basal state, acid secretion is maintained at an economically low level by the continuous inhibitory restraint exerted by somatostatin on the G cell (gastrin) in the antrum and on the ECL (histamine) and parietal cell (acid) in the fundus/body. During meal ingestion, maximal secretion may be achieved by removing the inhibitory influence of somatostatin while at the same time directly stimulating acid and gastrin secretion. This is accomplished, in large part, by activation of cholinergic neurons (Figure 4). Anticipation of a meal activates central neurons whose input is relayed via the vagus nerve to gastric intramural cholinergic neurons. In the fundus/body, ACh, released from cholinergic neurons, stimulates the parietal cell directly, as well as indirectly, by eliminating the inhibitory paracrine influence of somatostatin on parietal and ECL cells.<sup>53,122</sup> The resultant increase in histamine stimulates acid secretion directly via  $\text{H}_2$  receptors on the parietal cell and indirectly via  $\text{H}_3$  receptors that mediate suppression of somatostatin secretion (Figure 4).<sup>53,123</sup> Thus, histamine, acting via  $\text{H}_3$  receptors, amplifies the ability of secretagogues to stimulate acid secretion by suppressing somatostatin secretion. The net effect of cholinergic neurons is suppression of all paracrine inhibitory influence (ie, somatostatin) and enhancement of paracrine stimulatory influences (ie, histamine acting via  $\text{H}_2$  receptors) on parietal cells. There is some evidence that PACAP, a member of the glucagon/VIP superfamily of regulatory peptides, may participate in the regulation of acid secretion, but its precise physiologic role in this region of the stomach is uncertain.<sup>30,124,125</sup> PACAP is present in gastric mucosal nerves and is capable of releasing histamine from ECL cells and somatostatin from D cells. The net effect of exogenous PACAP on acid secretion has been reported to be either stimulation or inhibition, depending on the relative contributions of released histamine and somatostatin in each preparation.<sup>124,126,127</sup>

In antrum, cholinergic neurons stimulate gastrin secretion directly as well as indirectly by suppressing somatostatin secretion (Figure 4).<sup>37,38,41,128-139</sup> This is accomplished by a direct inhibitory effect of ACh on somatostatin secretion



as well as an indirect inhibitory effect mediated by suppression of ANP secretion (Figure 4).<sup>30,125,140</sup> In physiologic concentrations, gastrin stimulates parietal cells indirectly by enhancing histamine secretion.<sup>141,142</sup> In addition, protein activates GRP neurons that stimulate gastrin secretion directly (Figure 4).

As the meal empties the stomach, a number of paracrine and neural pathways are activated to restore the inhibitory influence of somatostatin in the fundus/body and antrum and hence restrain acid secretion (Figure 4). First, a stimulatory paracrine pathway linking gastrin to antral somatostatin cells is activated that acts to restore antral somatostatin secretion after release of gastrin.<sup>80</sup> Second, there is less activation of cholinergic neurons by anticipation of the meal as well as by protein and distention. Third, as distention decreases, VIP neurons are preferentially activated that stimulate somatostatin secretion.<sup>137</sup> Fourth, as the buffering capacity of the meal is lost, antral and fundic/body somatostatin cells are exposed to the full stimulatory effect of luminal acid. Fifth, amylin, released from D cells, stimulates somatostatin secretion.<sup>33</sup> The resultant increase in antral and fundic somatostatin secretion attenuates gastrin and acid secretion and eventually restores the basal interdigestive state. This state is marked by the continuous restraint exerted on G (gastrin), ECL (histamine), and parietal cells (acid) by contiguous somatostatin cells. A decrease in this restraint is sufficient to again initiate acid secretion.

#### *Perturbations in Acid Secretion Induced by HP*

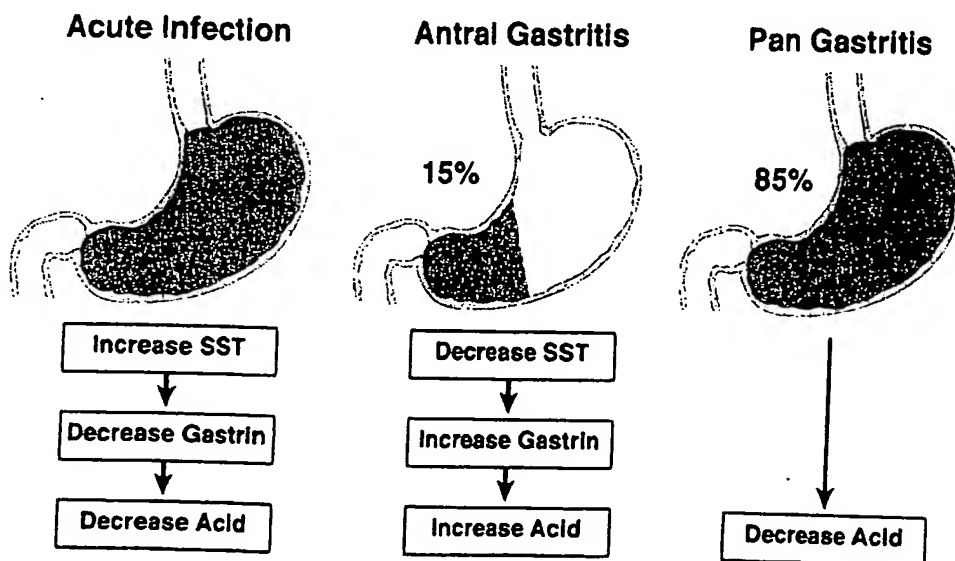
HP colonizes half the world's population and is a cause of acute gastritis, chronic gastritis, and gastroduodenal ulceration. Acute infection results in hypochlorhydria, whereas chronic infection results in either hypo- or hyperchlorhydria (Figure 5). Appreciation of the path-

ways discussed above provides some insight into the mechanisms whereby HP infection may lead to ulceration. Acute infection with HP is associated with hypochlorhydria.<sup>143-146</sup> The decrease in acid secretion is thought to facilitate survival of the organism and colonization of the stomach.<sup>147</sup> The mechanism whereby HP inhibits acid secretion is multifactorial and includes (1) direct inhibition of the parietal cell (and perhaps ECL cell) by a constituent of the bug (eg, vacuolating cytotoxin, lipopolysaccharide, or acid-inhibitory factor) and (2) indirect inhibition of parietal cell function as a result of changes in cytokines as well as hormonal, paracrine, and neural regulatory mechanisms.<sup>148-151</sup> HP itself inhibits human  $H^+K^+$ -ATPase  $\alpha$ -subunit gene expression.<sup>152</sup> It also elicits secretion of at least 2 cytokines, interleukin 1 $\beta$  and tumor necrosis factor- $\alpha$ , that directly inhibit parietal cell secretion.<sup>105</sup> In preliminary studies, we have shown that HP activates CGRP sensory neurons coupled to stimulation of somatostatin and thus inhibition of gastrin, histamine, and acid secretion.<sup>153</sup>

Chronic infection with HP may be associated with either decreased or increased acid secretion, depending on the severity and distribution of gastritis (Figure 5).<sup>154</sup> Most patients chronically infected with HP manifest a pangastritis and produce less than normal amounts of acid.<sup>155</sup> Reduced acid secretion, at the onset, is thought to be due to functional inhibition of parietal cells by either products of HP itself or, more likely, products of the inflammatory process, as discussed above for acute infection<sup>156,157</sup>; this is usually reversible upon eradication of the bug.<sup>158-160</sup> In such patients, HP may be protective against GERD, Barrett's esophagus, and esophageal adenocarcinoma as well as augment the antisecretory effect of PPIs.<sup>161,162</sup> Conversely, rebound acid hypersecretion

### *H pylori: Acid Secretion*

**Figure 5.** Model illustrating the consequences of *H pylori* infection on gastric acid secretion. Acute infection is associated with an increase in somatostatin (SST) and thus decrease in gastrin and acid secretion. Most patients chronically infected manifest a pan gastritis and also exhibit decreased acid secretion. In contrast, a minority of chronically infected patients manifest an antral-predominant gastritis and are predisposed to duodenal ulcer disease. These patients exhibit a decrease in somatostatin and a reciprocal increase in gastrin and acid secretion.



occurs in HP-eradicated patients when PPIs are discontinued, and this may unleash or exacerbate GERD, particularly in patients with large hiatal hernias.<sup>163,164</sup> Acid hypersecretion lasts at least 8 weeks and is due to hypergastrinemia-induced increases in parietal and ECL cell masses.<sup>165</sup> With time, atrophy of oxyntic glands with loss of parietal cells may occur, resulting in irreversible achlorhydria.

Approximately 10% to 15% of patients chronically infected with HP have antral predominant inflammation. These patients, who are predisposed to duodenal ulcer, produce increased amounts of acid as a result of reduced antral somatostatin content and elevated basal and stimulated gastrin secretion (Figure 5).<sup>166-168</sup> The mechanism by which somatostatin secretion is decreased is not known but may involve cytokines induced by the inflammation and/or the production of *N*-methyl histamine, a selective H<sub>3</sub>-receptor agonist, by HP.<sup>169,170</sup> One may speculate that the H<sub>3</sub>-receptor agonist could diffuse across the antral mucosa to interact with H<sub>3</sub> receptors on antral somatostatin cells, causing inhibition of somatostatin secretion, and, thus, stimulation of gastrin secretion.<sup>54</sup> Gastrin, in turn, stimulates histamine secretion from ECL cells leading to enhanced acid secretion. Both interleukin-8 and platelet-activating factor are up-regulated in HP-infected mucosa and are capable of stimulating gastrin release from isolated rabbit and canine G cells.<sup>171,172</sup>

### Duodenal Ulcer

Duodenal ulcer patients, as a group, have increased basal and stimulated acid production. Consequently, acid control has always been central to the management. Antacids were the first therapeutic approach used, but, to neutralize luminal acid adequately, they had to be dosed frequently leading to noncompliance and adverse effects.<sup>173,174</sup> Anticholinergic medications were used to delay gastric emptying and thus prolong the local effect of antacids.<sup>173</sup> These compounds, however, were nonselective in their antimuscarinic actions and caused gastrointestinal, urinary, central nervous system, and visual adverse effects. Potentially more selective antimuscarinics such as pirenzepine with greater M<sub>1</sub> selectivity and less nonspecific adverse effects were used in Europe but were never commercially available in the United States.<sup>175</sup>

Although antacids with high neutralizing capacity given 1 and 3 hours after meals and at bedtime could accelerate ulcer healing, pain was not relieved any better by such a regimen than by placebo.<sup>176</sup> Because ulcer disease could not be cured by antacids, recurrence and complications were common. These issues were addressed with surgery, the goal of which was to reduce acid secretion. The least extensive surgery involved performing a vagotomy to denervate the acid-producing area of the stomach along with a "drainage procedure," either pyloroplasty or gastroenterostomy. More extensive ulcer

surgery involved combining vagotomy with antrectomy, the latter to remove gastrin, the main hormonal stimulant of acid secretion.<sup>177</sup> The most extensive surgical approach was subtotal gastric resection. Sometimes patients underwent preoperative acid secretory testing, and, if high levels of acid were documented, more extensive resective surgery was done. In fact, the success of surgical "cure" of duodenal ulcer was generally thought to be related to completeness of vagotomy and extent of gastric resection.<sup>173,178</sup> Unfortunately, surgery proved not to be definitive (1%-10% recurrence rate) and produced its own set of problems including gastric stasis, nutritional deficiencies, altered bowel function, bile reflux gastritis and esophagitis, and gastric remnant cancer.

The development of cimetidine, the first H<sub>2</sub>RA, ushered in a new era of ulcer management.<sup>179</sup> Pills, for the first time, could improve ulcer healing at least as well as cumbersome antacids. H<sub>2</sub>RAs blocked both histamine-driven acid secretion and that elicited by gastrin, whose action is mediated primarily by release of histamine from ECL cells.<sup>180,181</sup> H<sub>2</sub>RAs were initially dosed 4 times daily, later twice daily, and eventually once daily. The fact that ulcers would heal quickly, even with once daily bedtime administration, drew attention to the importance of nighttime acid in the pathogenesis of duodenal ulcer.<sup>9</sup> Studies suggested that ulcer healing was related to nocturnal acid control—maintaining intragastric pH >3, a pharmacologic endpoint easily and predictably achieved by H<sub>2</sub>RAs.<sup>8</sup> In addition to healing duodenal ulcer, it became clear that continuous daily bedtime dosing of H<sub>2</sub>RAs could prevent ulcer recurrence.<sup>182</sup> Healing an ulcer with 8 weeks of "full dose" followed by indefinite treatment with "half dose" H<sub>2</sub>RA dosed at bedtime became the new gold standard for duodenal ulcer management. Elective acid-reducing surgery became less common. However, patient compliance with long-term acid suppressive medication, especially when symptoms no longer prompted dosing, was on occasion suboptimal and resulted in ulcer recurrence and complications, although to a far lesser degree than seen in the "BC" (before cimetidine) era. It was these patients who were referred for acid reducing surgery, mainly highly selective "parietal cell" vagotomy.<sup>183,184</sup>

Management of acid disorders was revolutionized when PPIs became available.<sup>185,186</sup> Because PPIs directly inhibit the acid pump, they are capable of reducing basal and stimulated acid secretion independent of stimulus. They are much more effective in controlling intragastric pH than H<sub>2</sub>RAs and have been shown to be more effective in healing duodenal ulcer and preventing recurrence.<sup>187</sup>

It is now recognized that most cases of duodenal ulcer are due to infection with HP, and HP is responsible for the perturbations in acid secretion observed in duodenal ulcer patients. Pentagastrin-stimulated peak acid output, an indicator of functional parietal cell mass, is increased



in HP-infected duodenal ulcer patients as is GRP-stimulated peak acid output, an indicator of the stomach's functional response to endogenous gastrin.<sup>168,188,189</sup> It is thought that suppression of somatostatin secretion by the infection may be the root cause for these changes (Figures 4 and 5). Eradication of HP restores somatostatin as well as basal and stimulated gastrin and acid secretion, over time, to normal in most individuals, thus providing a permanent cure for duodenal ulcer disease.<sup>167,168,188,190-192</sup>

### Gastric Ulcer

In contrast to duodenal ulcer, gastric ulcer patients, as a group, exhibit normal or decreased basal and stimulated acid production. This suggests that altered gastric mucosal defense may be the primary culprit and may explain the propensity for NSAID-induced ulcer to occur in the stomach. Gastric ulcers have been classified according to their location and concomitant association with duodenal ulcer.<sup>193</sup> Type I ulcers occur in the gastric body and are generally characterized by low acid secretion, particularly at night. These findings may reflect a greater degree and more generalized mucosal inflammation of the oxyntic mucosa with reduced functional parietal cell mass. Type II ulcers occur in the antrum and are characterized by low, normal, or high acid secretion. Type III ulcers occur within 3 cm of the pylorus, commonly accompany duodenal ulcer, and are characterized by high acid output. Type IV ulcers occur in the gastric cardia and are characterized by low acid secretion.<sup>194</sup> Thus, it appears that the more distant a gastric ulcer is from the pylorus the more likely acid secretion will be low. This concept formed the basis of gastric ulcer surgery whereby distal ulcers were traditionally managed by resection/drainage and vagotomy, whereas more proximal lesions were treated by resection alone.<sup>4,195</sup>

Medical therapy for gastric ulcer involves both removing the injurious agent (eg, NSAIDs or HP) and inhibiting acid secretion.<sup>187,196,197</sup> Healing correlates with duration of acid inhibitory therapy rather than degree of acid suppression during the day or night.<sup>198</sup> Thus, despite lower acid profiles in the setting of gastric ulcer, H2RAs and PPIs are often prescribed for longer periods of time (8-12 weeks) and at higher doses (generally double dose) than for duodenal ulcer to ensure healing.<sup>187</sup> Unlike duodenal ulcer, gastric ulcers may be malignant, especially in the setting of HP and achlorhydria. Thus, gastric ulcers should be biopsied and healing documented. Recurrence can be prevented by avoiding NSAIDs, eradicating HP, and/or maintenance antisecretory therapy. As previously discussed, acid secretion may increase after elimination of HP.<sup>160</sup>

"Stress ulcers" are most commonly located in the proximal stomach, occur in the setting of critical illness and multiple organ failure, and are thought to result from mucosal ischemia and altered mucosal defense.<sup>199</sup> The

latter is central to the pathogenesis of stress ulcer, so it will be discussed more fully in a subsequent review of mucosal defense. Despite the fact that acid secretion is variable, antisecretory medications, by improving the imbalance between aggressive and defensive factors, prevent stress ulcers and the complication of bleeding.<sup>199-202</sup>

### GERD

With the decreasing prevalence of ulcer disease, GERD has emerged as the most important acid-related disorder.<sup>203,204</sup> Because its pathogenesis involves acid in the wrong place, rather than too much acid, treatments have included elevation of the head of the bed, foaming agents, medications to enhance lower esophageal sphincter pressure, and antireflux surgery; unfortunately, all but surgery are often ineffective.<sup>205</sup> Consequently, medical treatment of GERD has focused on acid inhibition, specifically maintaining pH >4 in the esophagus for as much of the day and especially the night as possible.<sup>18,206</sup> This goal is best achieved with PPIs because antacids have a short duration of action, and chronic use of H2RAs leads to tachyphylaxis.<sup>207</sup>

PPIs are superior to H2RAs for treating heartburn and healing erosive esophagitis.<sup>21,208,209</sup> More severe grades of erosive esophagitis, Los Angeles grades C and D, are more difficult to heal and may require longer treatment duration and higher doses of PPIs.<sup>21,210</sup> Such a dose response for symptom control is less evident, especially in nonerosive reflux disease.<sup>211,212</sup> Furthermore, extending duration of therapy or increasing the dose in "non-responders" will not necessarily improve treatment efficacy.

Nighttime or supine acid reflux has been linked to more severe esophagitis, complicated GERD, and extra-esophageal reflux manifestations.<sup>213</sup> Nocturnal acid secretion is low in volume but highly concentrated and may be difficult to inhibit with once daily PPI treatment.<sup>214</sup> Nocturnal acid breakthrough, a situation in which intragastric pH (not intraesophageal) falls to and remains <4 for more than 1 hour overnight occurs in 73% of both GERD patients and normal volunteers.<sup>215</sup> Several strategies have been proposed to manage nighttime acid including administering the once daily PPI before dinner, twice daily dosing of PPI (before breakfast and dinner), adding an H2RA at bedtime to a regimen of once or twice daily PPI, or prescribing an immediate release PPI at bedtime.<sup>216,217</sup> Although these approaches are successful to varying degrees in controlling nocturnal acid secretion, none have been shown conclusively to improve GERD outcomes in the short- or long-term.

GERD is a chronic condition that requires long-term treatment in most individuals. Maintenance acid suppression seems to be the most effective long-term medical approach. As with acute healing, preventing relapse is best achieved with PPIs, with full dose being better than half dose.<sup>19</sup> In patients who experience breakthrough GERD symptoms, compliance, appropriate timing of

medications, and lifestyle modifications should be emphasized. Once heartburn is under control, many patients will take their medications on demand rather than daily, as prescribed.<sup>218</sup> Others take the PPIs inappropriately, ie, between meals or at bedtime.<sup>219</sup> As discussed previously, PPIs are most effective when taken before meals.<sup>114</sup>

The role of HP eradication in the management of GERD remains controversial, and there is no compelling reason to test for HP in patients with GERD.<sup>220</sup> It is unlikely that cure of infection will positively impact symptoms to any great degree, and there is evidence that it might actually worsen symptoms.<sup>221</sup> Most patients chronically infected with HP manifest a pangastritis and produce less than normal amounts of acid. In these patients, HP infection may actually protect against GERD (also, Barrett's esophagus and esophageal adenocarcinoma), and eradication may augment acid secretion.<sup>161,222,223</sup> Not only may HP protect against GERD, but HP may make GERD more responsive to treatment by augmenting the acid-inhibitory effect of PPIs.<sup>224</sup> Thus, eradication of HP has the potential to both increase acid secretion and decrease the efficacy of PPIs, thereby making GERD more difficult to control.<sup>160,223</sup>

### Gastric Acid Hypersecretion

There are a number of uncommon conditions in which gastric acid secretion is abnormally high and ulcers develop. In patients with systemic mastocytosis, high histamine levels, as a consequence of increased numbers of mast cells, continuously stimulate parietal cells to secrete acid.<sup>225</sup> When a portion of gastric antrum is retained in the afferent remnant after antrectomy with Billroth II anastomosis, it is bathed in alkaline secretions leading to decreased somatostatin secretion, hypergastrinemia, increased acid production, and anastomotic ulcers.<sup>78,96,226</sup> Acid hypersecretion can also result from chronic hypercalcemia of any cause because calcium directly stimulates gastrin secretion from human G cells and acid secretion from parietal cells.<sup>227,228</sup>

The best characterized acid hypersecretory condition is ZES.<sup>17,229</sup> ZES is caused by a gastrin-producing tumor (gastrinoma) that results in gastric acid hypersecretion. Gastrin, synthesized by the tumor, is secreted into the bloodstream where it binds to CCK<sub>2</sub> receptors on acid-producing parietal and histamine-containing ECL cells to induce secretion as well as proliferation. The clinical correlate of the proliferation is rugal hypertrophy with prominent gastric folds. ZES should be suspected in patients with refractory erosive esophagitis, multiple peptic ulcers, ulcers in the distal duodenum or jejunum, complicated ulcers, recurrent ulcers after acid-reducing surgery, ulcers associated with diarrhea, and a family history of MEN-1 or any of the endocrinopathies associated with MEN-1.<sup>230</sup> Approximately 25% of patients with ZES have MEN-1, an autosomal dominant disorder char-

acterized by pancreatic endocrine tumors, pituitary adenomas, and hyperparathyroidism; in the latter, hypercalcemia can further stimulate acid secretion. Diarrhea may be a prominent symptom, occurring in 65% of ZES patients, and is due to the large volume of acid, which inactivates pancreatic lipase and damages the proximal small bowel absorptive mucosa.

Diagnosis of gastrinoma includes serum gastrin radioimmunoassay, secretin stimulation test, and, more recently, somatostatin receptor scintigraphy and endoscopic ultrasound. The basis of the secretin test is that normally, in the antrum, somatostatin cells tonically restrain gastrin secretion from G cells. Secretin stimulates the G cell directly and, at the same time, inhibits the G cell indirectly by stimulating somatostatin secretion; the effect of the latter dominates, and gastrin is not stimulated. Because the gastrinoma does not contain functionally coupled somatostatin cells, the effect of secretin is solely stimulation of gastrin secretion from the tumor.<sup>231-233</sup> After an overnight fast, 0.4 µg/kg secretin is given intravenously over 1 minute. Two baseline values are obtained then blood is collected at 1, 2, 5, 10, and 30 minutes. An increase in gastrin of more than 200 pg/mL over the preinjection value indicates ZES; more than 90% of ZES patients exhibit an increase in gastrin at 2 or 5 minutes. Almost all gastrinomas contain somatostatin receptors, and somatostatin receptor scintigraphy using [<sup>111</sup>In-DTPA-Dphe1]-octreotide is considered the initial localization study of choice, with a 71% sensitivity and 86% specificity for primary tumors and 92% detection for metastatic disease.<sup>234,235</sup>

Total gastrectomy, initially the treatment of choice to prevent life-threatening complications, has been abandoned in favor of antisecretory therapy and selective surgical resection of the gastrinoma. H2RAs represented the first viable medical therapy to control acid hypersecretion. Unfortunately, increasingly large doses were required, and acid suppression was often inconsistent. Consequently, gastrinoma enucleation or parietal cell vagotomy was often added to suppress acid secretion. The goal of antisecretory therapy is to reduce acid secretion to less than 10 mEq/h (<5 mEq/h if patient underwent prior gastric acid-reducing surgery) as measured 1 hour before the next dose.<sup>230</sup> Today, PPIs are the antisecretory therapies of choice and are able to control acid secretion and prevent complications in most patients with ZES, although very high doses of medication (eg, omeprazole 120 mg/day) may be necessary, especially in patients with MEN-1.<sup>236</sup>

### Safety of Acid Suppression

Acid suppression continues to be the major medical strategy to treat acid-peptic disorders. For decades, millions of patients have had their acid neutralized or inhibited effectively and safely first with antacids then with H2RAs and now with PPIs. Because antacids are

rarely used anymore as primary therapy for acid-related disorders, their adverse effects, including diarrhea; constipation; interference with drug absorption; and rare renal, metabolic, and acid base disturbances are only of historical importance.<sup>6,237</sup>

H2RAs are generally well tolerated with adverse effects observed in 1.5% of treated patients compared with 1.2% of placebo patients.<sup>181</sup> Rare adverse effects include mental confusion (<0.2%), gynecomastia, interstitial nephritis (0.001%), interference in the absorption of drugs requiring an acid environment such as ketoconazole and itraconazole, and cytochrome P450 interactions. Although cimetidine is capable of inhibiting the catalytic activity of one or more cytochrome P450 enzymes (CYP1A2 and CYP2C19), clinically significant drug interactions are very rare.

PPIs are safe drugs, but concerns have been voiced regarding potential adverse effects related to hypergastrinemia, rebound acid hypersecretion, malabsorption, infection, and drug interactions. Since the introduction of omeprazole, there was concern that PPI-induced hypergastrinemia may have untoward effects. In rats, ECL cells, under stimulation of gastrin, evolve through hyperplasia to dysplasia and eventually to carcinoid tumors.<sup>84,238,239</sup> Humans respond to a decrease in luminal acid with a lesser increase in serum gastrin than rats and do not develop gastric carcinoids unless in the settings of severe atrophic gastritis (pernicious anemia) or ZES associated with MEN-1.<sup>240,241</sup> The possibility exists that hypergastrinemia could exert trophic effects outside of the stomach and influence the growth of premalignant and malignant cells because CCK<sub>2</sub> receptors have been identified in a variety of tissues including Barrett's esophagus, stomach, pancreas, and colon as well as in cancers derived from these and other tissues (esophageal adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, neuroendocrine tumors, colon adenocarcinoma, medullary thyroid cancer, small cell lung cancer, leiomyosarcoma, and stromal ovarian cancer).<sup>242-245</sup> Although there is no convincing evidence that hypergastrinemia per se induces neoplasia, the possibility exists that it might accelerate the growth and invasiveness of cancers harboring its receptors.<sup>70,246-249</sup>

In humans, there is a prolonged rebound hypersecretion in HP-negative individuals after discontinuation of a PPI, with increases in both basal and maximal acid output.<sup>163,165,250</sup> The phenomenon occurs after as little as a 2-month course of therapy and lasts at least 2 months after the PPI is stopped. The pathophysiology is thought to be due to the trophic effect exerted by gastrin on histamine-containing ECL cells leading to their hyperplasia and hypertrophy.<sup>83,251,252</sup> The reason the phenomenon does not occur in HP-positive individuals may be due to the fact that HP as well as cytokines induced by the inflammatory infiltrate inhibit acid secretion and thus mask the rebound.<sup>148,149,151,154,156</sup> The clinical rele-

vance of rebound hypersecretion is that patients may become physiologically addicted to PPIs. That is, the increased acid secretion after discontinuation of PPIs may induce or exacerbate acid-peptic disorders such as GERD and dyspepsia causing patients to resume antisecretory therapy. One way to prevent this from happening might be to, instead of abrupt discontinuation, taper the PPI and switch to tapering doses of H2RAs over a period of 2 months.

Chronic hypochlorhydria induced by PPIs could interfere with absorption of nutrients such as vitamin B-12, iron, and calcium. Several reports indicate that chronic use of PPIs may result in low levels of vitamin B-12 probably by impairing acid-induced release of B-12 from food. The recommended daily allowance of B-12 is 2 µg/day, and total body stores are 2.5 mg. Vitamin B-12 deficiency because of PPIs is rare, probably because acid secretion is not completely inhibited and the body has relatively large stores.<sup>253-255</sup>

Acid is thought to facilitate dietary iron absorption. Exposure to acid frees heme iron from its apoprotein and converts nonheme iron, which is largely in the form of ferric hydroxide, to the absorbable ferrous form. PPIs have been used to decrease iron absorption in patients with hereditary hemochromatosis.<sup>256</sup> Despite the fact that medicinal iron is in the ferrous form, there is a single report of 2 patients in whom iron deficiency did not respond to treatment until PPIs were discontinued.<sup>257</sup>

In a recent population-based study, long-term PPI therapy was implicated as a cause of hip fractures in older women.<sup>258</sup> Although the relative risk of fractures increased with dose and duration of acid suppression, the absolute risk of fractures remained very low. The basis for this is not known but may involve interference with calcium absorption or bone metabolism.<sup>259</sup> This finding requires confirmation before patients receiving benefit from PPIs are advised to stop them.

Gastric acid protects against bacterial overgrowth and enteric infection.<sup>260-263</sup> Two recent epidemiologic studies have implicated PPIs as a risk factor for the development of community, as well as hospital-acquired *Clostridium difficile*-associated disease.<sup>264,265</sup> Because ingested *C difficile* spores are not susceptible to destruction by acid, these findings may not represent true cause and effect. It is likely that the finding was confounded by the fact that patients receiving PPIs were more likely to be sicker and more susceptible to infection when exposed to antibiotics. A similar argument may be advanced for the association between acid suppressive medications and community-acquired pneumonia.<sup>266,267</sup> In these studies, confounders such as concomitant pulmonary disease and severe GERD, which might predispose to pneumonia, were not controlled.

All PPIs are metabolized by the cytochrome P450 family of enzymes. There had been some concern that omeprazole and other PPIs, through inhibition of certain

cytochrome P450 enzymes, might increase the half-life of certain medications such as theophylline, phenytoin, diazepam, and warfarin.<sup>268-270</sup> Because PPIs are in the bloodstream for a relatively short time (plasma half-life, ~1 hour) and are relatively weak inhibitors of cytochrome P450, clinically relevant drug-drug interactions are extremely rare (<0.1 per million packages) and do not constitute a major clinical risk.<sup>271</sup>

## Conclusion

Gastric acid remains an important pathogenic factor for a variety of common upper gastrointestinal disorders. Over time, the prevalence as well as the management of these disorders has changed. Generations of gastroenterologists and surgeons measured acid output and tailored medical and surgical treatment of peptic ulcer disease based on the results. The management of these disorders has been revolutionized by the introduction of potent antisecretory medications and the understanding of the role of HP in their pathogenesis. As a result, the quantitative measurement of gastric acid secretion, for the most part, has become obsolete. Nevertheless, gastric acid secretion and its inhibition will continue to be important to gastroenterology as a specialty, at least for the foreseeable future. Have we reached the zenith in our understanding of gastric acid physiology and the development of pharmacologic treatments for acid-peptic disorders? We do not think so. These disorders remain prominent, and there is much still to be discovered by future clinical and basic investigators.

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Address requests for reprints to: Mitchell L. Schubert, MD, McGuire VAMC, code 111N, Gastroenterology Division, 1201 Broad Rock Blvd, Richmond, Virginia 23249. e-mail: Mitchell.Schubert@va.gov; fax: (804) 675-5816.

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## Antacid therapy

JUAN-R. MALAGELADA and  
GERALD L. CARLSON

Gastroenterology Unit, Mayo Clinic, Rochester,  
MN 55901, USA

The major goals of antacid therapy are: a) to reduce the acidity of gastric contents and the load of acid into the duodenum and b) to diminish peptic activity by increasing the luminal pH above that optimal for proteolysis. In this review we will discuss the physicochemical and pharmacological basis of antacid therapy, its effect on gastric function, and its efficiency in achieving the above goals. We will also refer to other properties of common antacids, which may be of clinical value in special circumstances: bile acid binding and effects on pancreatic, gallbladder, and intestinal function.

Common commercially available antacids consist of sodium bicarbonate, calcium carbonate, magnesium hydroxide, or aluminum hydroxide, either alone or in combination. Because there are significant chemical and physical differences between these compounds and the products of their reaction with hydrochloric acid, the chemistry and pharmacology of each will be reviewed. Many of these concepts also apply to a variety of other compounds incorporated into some commercial antacid preparations, but due to space limitations these cannot be discussed individually.

### PHYSICOCHEMICAL PROPERTIES AND PHARMACOLOGY

Sodium bicarbonate is the salt of a weak acid (carbonic acid) and a strong base (sodium hydroxide). The compound is soluble in water (6.9 g/dL at 0°C) and reacts with HCl to form NaCl, H<sub>2</sub>O, and CO<sub>2</sub>. Loss of CO<sub>2</sub> makes this reaction irreversible under physiologic conditions. The reaction product, NaCl, is very water soluble (35.7 g/dL, 0°C), and no hydrolysis to NaOH is observed. Ingestion of sodium bicarbonate produces a base excess equivalent to the amount ingested because of the failure of NaCl to react with carbonate, phosphate, or hydroxide ions later in the

gastrointestinal tract. Thus there is a risk of significant alkalosis from its frequent and prolonged use.

Calcium carbonate is analogous to sodium bicarbonate, but is much less soluble (0.0015 g/dL). Reaction with HCl yields CO<sub>2</sub>, H<sub>2</sub>O, and CaCl<sub>2</sub>, again a highly water-soluble salt. Unlike sodium, however, the divalent Ca ion will reform (and precipitate) calcium carbonate in the presence of aqueous carbonate or bicarbonate (from which carbonate can be formed by reaction with hydroxide ion). Calcium phosphate may also be precipitated if phosphate ion is present; in both cases, the reaction is driven to the right by the low solubility product of the calcium carbonate or phosphate. Thus the essential difference between sodium and calcium carbonate is that the reaction of CaCO<sub>3</sub> with HCl is effectively reversible under physiologic conditions; it must be emphasized, however, that the forward and reverse reactions occur at different times, in anatomically distinct organs, and in different chemical milieus. To the extent that calcium is reconverted to the carbonate or phosphate in the gut, an equal amount of acid and base will have been used. Alkalosis will therefore be of lesser magnitude than with sodium bicarbonate. However, since some calcium will be absorbed by the proximal small bowel, the reverse reaction cannot be equal to the neutralization and, furthermore, hypercalcemia may become a problem in chronic users (Ivanovich et al. 1967, Morrissey & Barreras 1974).

Magnesium hydroxide is the other antacid derived from a group II metal. Like calcium carbonate, Mg(OH)<sub>2</sub> is poorly soluble (0.0009 g/dL, 18°C); the chloride produced is quite soluble (54.25 g/dL, 20°C) and both the carbonate and the phosphate are insoluble. Because the reaction to form MgCl<sub>2</sub> produces only water, the reaction is theoretically reversible; in practice, the hydrolysis of Mg<sup>2+</sup> requires a pH above 8 (Derek 1963) and so may be ignored in the bowel. Presumably magnesium behaves like calcium in the bowel and reacts with phosphate or bicarbonate to produce the insoluble magnesium salts which are excreted. However, about 1/3 to 1/4 of the total amount of magnesium ingested is absorbed. In patients

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with renal failure (thus with limited ability to excrete magnesium), this poses a significant risk.

Aluminum hydroxide is the only antacid derived from a group III element, and therefore differs from all the others.  $\text{Al}(\text{OH})_3$  is amphoteric and relatively insoluble in water. Although  $\text{AlCl}_3$  is water soluble, the hydrated trivalent cation is quite acidic and hydrolysis becomes significant in the physiologic pH range, leading to the formation of various intermediate chlorohydroxides. The situation is further complicated by the slow approach to equilibrium and because the cation may form complex hydrated ions such as  $[\text{Al}_2(\text{OH})_2]^{4+}$  and  $[\text{Al}_3(\text{OH})_4]^{5+}$ , both of which are known to exist in basic crystalline salts (Aveston 1965). This pH-dependent formation of intermediate chlorohydroxides thus lowers the effective acid-neutralizing capacity of  $\text{Al}(\text{OH})_3$  gels (to about 80 % of the theoretical value) in a complex, pH-sensitive fashion (Deering et al. 1977). The situation is further complicated by the probable formation of the insoluble phosphate in the gut. Aluminum ion is poorly absorbed by the small bowel but detectable plasma aluminum concentrations after aluminum-containing antacids have been reported (Kuehny et al. 1977). Circulating aluminum is cleared by the normal kidney; increased deposition in tissues has been observed in chronic renal failure (Recker et al. 1977).

Since the chemical properties of aluminum hydroxide and magnesium hydroxide produce differences in the "in vivo" neutralizing effectiveness of antacids, these should be taken into account when choosing antacid preparations based on "in vitro" total neutralizing power. Both antacids are often found commercially as a combination gel, to counterbalance their opposite effects on bowel habit (see later). These gels react relatively slowly with gastric acid, and profound alterations in acid base balance are not to be feared except with massive administration.

#### "IN VITRO" EVALUATION OF ANTACIDS

Fordtran et al. (1973) popularized several years ago a standardized procedure for testing antacids "in vitro". This test was based on the capacity of an antacid solution to neutralize acid added to it at a constant rate, so that the pH of the

solution would be maintained constant at 3.0. At this pH, 99 % of a 100 mM-solution of HCl would have been neutralized. The conditions for the test were chosen arbitrarily but they were felt to reflect "in vivo" measurements more closely than would a simple determination of the total neutralizing capacity by end-point titration. This may be due to the fact that it evaluates the speed with which the antacid combines with acid, as well as the total neutralizing capacity (to pH 3.0 as end point). As we will discuss later, an antacid which reacts too rapidly with acid will have an intense but also transient neutralizing effect in contrast to the sustained effect of a slower one. However, it is important to recognize that no form of "in vitro" testing can actually approximate the real behavior of antacids in the stomach, which depends as much on gastric emptying as it does on neutralizing kinetics.

#### "IN VIVO" EVALUATION OF ANTACIDS

It has long been recognized that antacids ingested on an empty stomach are quickly evacuated and only partially utilized. Thus their acid-neutralizing effects are brief (Grossman 1956). In contrast, administration of antacid after a meal leads to better utilization of the antacid and a more prolonged action (Fordtran & Collins 1966). For this reason, antacids are clinically prescribed according to schedules linking their administration to the time of ingestion of a meal.

Sodium bicarbonate or baking soda is one of the oldest known antacids. It reacts almost instantaneously with acid. Simmons et al. (1978) have recently shown that bicarbonate administered postprandially in conventional doses raises the intragastric pH to 7 to 8, explaining the immediate symptomatic benefit experienced by many patients. However, as expected, the effects are of short duration because the antacid is rapidly consumed and new acid is secreted rapidly, lowering intragastric pH. Further, bicarbonate produces  $\text{CO}_2$  which increases gaseous feeling, has a high sodium content - which may be contraindicated in some patients - and tends to produce a base excess.

Calcium carbonate is a potent antacid with a rapid onset of action and a relatively prolonged

effect. The main disadvantage of calcium carbonate is that it causes acid rebound (Fordtran 1968, Barreras 1970). This is due to the effect of calcium ion which has the capacity of stimulating the parietal cells directly (Holtermüller et al. 1974) through gastrin release (Levant et al. 1973) and indirectly by causing hypercalcemia (Malagelada et al. 1976). The magnitude of the acid rebound is not great and its effects might theoretically be counteracted by frequent administration of the antacid. However, there still would be concern about the effects of prolonged stimulation of parietal cells.

Aluminum and magnesium hydroxides constitute the basis of many commercial antacids. There is no evidence that these substances cause significant acid rebound. The relative proportions of magnesium and aluminum are adjusted by different pharmaceutical manufacturers to lean either toward causing looser stools or constipation. The characteristics of gel on which aluminum and magnesium hydroxides are incorporated also vary depending on the manufacturer, and this may perhaps influence its capacity to mix with gastric contents and react with acid.

When an antacid mixture of aluminum and magnesium hydroxides, such as Maalox®, is given to patients after a meal, it produces a rather sustained, though somewhat fluctuating increase of intragastric pH (Deering & Malagelada 1977) (Figure 1). The time of administration should be carefully chosen, for it is necessary to take advantage of the elevation of intragastric pH produced by the diluting and buffering action of the meal itself. By the end of the first postprandial hour, the in-

tragastric pH is rapidly declining and at that time ingestion of a dose of antacid will be utilized most efficiently to reduce gastric acidity. Because of the slower neutralization process, the gastric pH, in contrast to what is observed with sodium bicarbonate, does not get up to 7 or 8 but, on the other hand, the effect is more prolonged. By the end of the third postprandial hour the pH is declining again since the first dose of antacid has already been partially consumed or emptied. At this time, a second dose of the antacid raises the pH again for at least another hour – a total of 4 hours after the meal. During daytime, it would be expected that another meal and another cycle of antacid administration would follow at regular intervals, thus keeping the intragastric pH almost continuously elevated.

The dose of antacid to be administered has been a subject of controversy. Obviously the more antacid and the higher its neutralizing power the better – but limitations exist on the amount that patients accept as convenient or even bearable. For most commercial preparations of aluminum and magnesium hydroxides, 1 ounce, 1 and 3 hours after meals and at bedtime is about as much as most patients will tolerate. Higher or more frequent doses risk poor compliance, a common problem with antacid therapy (Roth & Berger 1960), and increase the risk of unpleasant side effects. Fordtran has proposed tailoring the dosage of antacid to acid secretory capacity (Fordtran et al. 1973). This, however, is not practical since patients with duodenal ulcer are not invariably subjected to gastric secretory tests. Furthermore, as we expressed earlier, the efficacy of the neutralizing process depends on gastric emptying of the antacid as well as on gastric acid secretion, and measuring the former is not feasible in routine clinical practice.

#### UTILIZATION OF ANTACID AND ITS EFFECTS ON DUODENAL ACID LOAD

The development of new methodology has allowed the evaluation of the "in vivo" effects of antacids beyond simple determinations of gastric pH and titratable acidity. It is now possible to quantify the action of antacids on postprandial gastric secretion and emptying and to closely monitor the neutralizing reaction in the stomach.

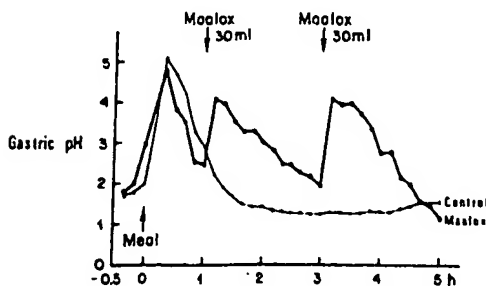


Figure 1. Effect of liquid aluminum and magnesium hydroxides (Maalox®) on postprandial gastric pH in patients with duodenal ulcer. Modified from Deering and Malagelada (1977).

Measuring the effect of antacids on duodenal acid load is particularly important since reduction of duodenal acid load is the major aim of antacid therapy in duodenal ulcer. Further, duodenal acid load depends not only on the efficiency of neutralization but also on gastric secretion and emptying. Thus, it is possible to measure the fraction of ingested antacid consumed by neutralization with gastric acid and the fraction emptied from the stomach before it has had a chance to react with acid. This is a quantitative assessment of the utilization of antacid. Such measurements are only available to date for a combination of aluminum and magnesium hydroxides (Maalox®) studied in our laboratory (Derek 1963, Deering & Malagelada 1977). Indirect data is also available for other antacids (Fordtran et al. 1973).

As observed in Figure 2, for about 1 hour after ingestion of a meal, negligible amounts of  $H^+$  ion enter the duodenum. Although this would, of course, depend a great deal on the type of meal and patient studied, it probably applies to some extent to most common therapeutic situations. The low duodenal  $H^+$  ion load is due to buffering and dilution of acid by meal protein. In other words, acid which leaves the stomach during the early postprandial period does so combined with food. Buffered  $H^+$  probably has little injurious effect on the duodenal mucosa. After the first hour the effect of the meal is rapidly diminishing and if no therapy is given, duodenal acid load sharply rises and will remain high for the next several

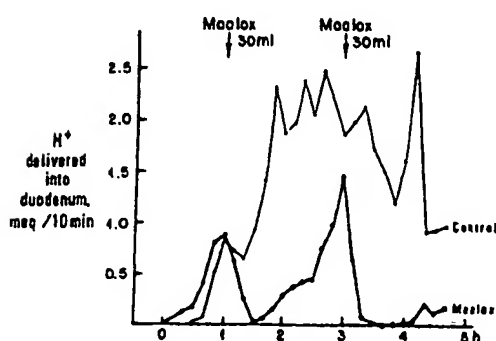


Figure 2. Effect of liquid aluminum and magnesium hydroxides (Maalox®) on postprandial delivery of  $H^+$  ion into the duodenum in patients with duodenal ulcer. Modified from Deering and Malagelada (1977).

hours. However, the two doses of Maalox® spaced 1 and 3 hours after the meal produce a marked reduction in  $H^+$  duodenal load. As observed with the intragastric pH, there is some fluctuation, with the least effect being observed during the second half of the third hour and the maximum effect, immediately after administering each dose.

The efficiency of antacid therapy, as measured concomitantly in these studies, is remarkable. A mean 127 meq of antacid was consumed in the stomach (range 93-138) out of a possible total 162 meq given (60 ml of liquid antacid). This represents a mean efficiency of about 80%. The first dose of antacid, given at 1 hour after the meal, was utilized more efficiently and emptied more slowly than the second dose given 3 hours after the meal. These results suggest that a further 20% of total antacid capacity could be utilized if antacid could be prevented from leaving the stomach before it has completely reacted with acid. Others have suggested that simultaneous administration of anticholinergic agents, which delay gastric emptying, as well as decreasing gastric secretion, would potentiate the action of antacids and increase their utilization. Some experimental support for this concept exists but further evidence would be needed before it can be recommended for routine clinical practice.

#### EFFECT OF ANTACID THERAPY ON GASTRIC FUNCTION

The effect of antacids on gastric function is an important aspect of antacid pharmacology. Since intragastric and intraduodenal pH play a key role in regulating gastric secretion and emptying, it is not unexpected that changes in gastric and duodenal acidity induced by antacid therapy would affect gastric secretion and emptying as well as gastrin release (Walsh et al. 1975). Additional effects might be due to certain constituents of the antacids, such as calcium, magnesium, or aluminum ions.

In our laboratory, we have recently measured the effects of aluminum and magnesium hydroxides on postprandial gastric secretion and emptying. We found that administration of 1 ounce of liquid Maalox®, 1 and 3 hours after a meal, significantly increased gastric acid output, by

5% as an average. This means that the quantity of acid available for neutralization after the antacid was greater than if no antacid had been given; further evidence that the actual conditions on which antacids act cannot easily be predicted "in vitro" or by measurements of gastric acidity. In the case of aluminum and magnesium hydroxides this increase in gastric secretion is mostly due to abolition of pH-dependent feedback inhibition of gastric secretion stimulated by the meal. The same would apply to sodium bicarbonate (Walsh et al. 1975). There is no evidence that the aluminum ion has any direct stimulatory effect on gastric secretion. Magnesium might have some stimulatory effect, but this is probably a weak one (Christiansen et al. 1975, Brodie et al. 1977). In contrast, intraluminal calcium is a well-known stimulus to gastric secretion and it is known to cause acid rebound. Although not yet quantified, it seems likely that postprandial gastric secretion after calcium carbonate increases relatively more than with aluminum and magnesium hydroxides since one should add the direct stimulatory effects of the calcium ion to the decrease in acid feedback inhibition. If this assumption is true, then the quantity of acid actually neutralized by calcium carbonate "in vivo" is probably much larger than would be predicted by the acid response to a placebo. In patients with the milk-alkali syndrome, the hypercalcemia could add to the stimulation of gastric secretion. However, it is debatable whether chronic hypercalcemia has the same gastric secretagogue action that has been observed with acute hypercalcemia.

The increase in gastric secretion produced by antacids means not only an increase in the amount of acid available for neutralization but also a parallel increase in the volume of gastric juice. Theoretically, the stomach confronted by an increased load of acid would have at least two ways to dispose of it. One way would be to increase the absolute rate of delivery of gastric contents into the duodenum so that the total volume of gastric contents remains constant. Another way would be to maintain constant the absolute rate of emptying but expand intragastric volume to accommodate temporarily the increased volume load. Our studies on postprandial gastric function after administration of aluminum and magnesium hydroxides

suggest that the latter hypothesis is true: intragastric volume increases whereas duodenal volume load remains constant.

Hurwitz et al. (1976), employing an external gamma camera to monitor the fractional gastric emptying of a radioactive marker, found delayed evacuation after aluminum hydroxide but not after non-aluminum-containing antacids of similar or greater neutralizing power. This suggests that aluminum-containing antacids have an inhibitory effect on motility besides their effect on gastric secretion. These observations are relevant to antacid pharmacology in relation to other substances administered concomitantly with antacids. One would expect that these substances would be diluted in the stomach and their emptying retarded by the effects of antacids on gastric function. Obviously, delayed emptying would influence absorption and times of peak serum levels as well as the level itself.

Just the opposite situation (Figure 3) is observed with cimetidine administration, which reduces gastric secretion with a contraction in gastric volume while maintaining a normal fractional gastric emptying (Longstreth et al. 1977). This may explain why in patients with pancreatic insufficiency cimetidine administered together with pancreatic

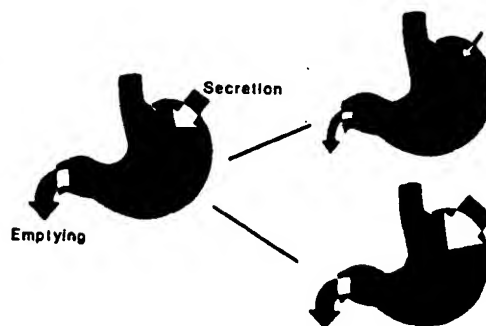


Figure 3. Diagrammatic representation of the effects of antacids or cimetidine on postprandial gastric secretion-emptying interactions. On the left, a hypothetical steady-state situation is represented where emptying balances secretion and intragastric volume remains stable. On the right above, the characteristic effect of cimetidine is represented: secretion is inhibited whereas intragastric volume and emptying are reduced proportionally. Fractional gastric emptying remains unchanged. On the right below, the effect of aluminum and magnesium hydroxides: secretion is stimulated, absolute emptying rates are unchanged, and intragastric volume increases. Thus, fractional gastric emptying is reduced.



enzyme supplements causes much greater concentration of exogenous enzymes in the duodenum than when antacids are used as adjuvant therapy (Regan et al. 1977).

#### CLINICAL EFFECTIVENESS OF ANTACIDS

The effectiveness of antacid therapy in duodenal or gastric ulcer has been debated for years. Until not long ago, the tide of opinion seemed to be leaning towards skepticism about the efficacy of these agents, supported by the negative results of several studies (Baume & Hunt 1969, Butler & Gersh 1975, Hollander & Harlan 1975). Yet, more recently, data strongly supporting the effectiveness of antacids in duodenal ulcer disease have been acquired.

Peterson et al. (1977) reported the results of a double-blind controlled trial employing an intensive antacid regimen (1 ounce of an aluminum-magnesium hydroxide preparation taken 1 and 3 hours after each meal and at bedtime) versus a placebo. These investigators found that antacid therapy significantly accelerated the healing of duodenal ulcer. After four weeks of therapy 78 % of patients had endoscopically-proven healing vs 45 % for placebo, a statistically significant difference. From a prophylactic standpoint, Hastings et al. (1978) found that neutralization ( $\text{pH} > 3.5$ ) of gastric contents by oral administration of relatively large quantities of antacids prevented the development of stress ulcer in critically ill patients. Several comparative studies show that antacids, when properly utilized, are equivalent to other available therapies (see later).

Several reasons may explain the apparent discrepancies between the results of these studies, which support the efficacy of antacid therapy and the older studies which did not:

- Many of the early studies utilized doses of antacids which were smaller than that needed to obtain the degree of reduction in acidity apparently required for a full therapeutic effect.

- They might have employed preparations like calcium carbonate which, despite an excellent neutralizing capacity, cause acid rebound.

- Proper dosage schedule is critically needed to coordinate antacid administration with meals and taking optimal advantage from them.

- Techniques for designing and carrying out therapeutic controlled trials have improved with time.

#### ANTACIDS VERSUS OTHER THERAPEUTIC AGENTS IN DUODENAL ULCER

Antacids, of course, neutralize acid which has already been secreted as opposed to other agents such as cimetidine or anticholinergics which inhibit acid secretion. Despite different mechanisms, as far as duodenal ulcer is concerned, all these different therapies have a common goal, namely, to reduce duodenal acid load. Comparisons between them may be referred to this parameter as a normalizing index.

We have examined the effect of accepted therapeutic doses of cimetidine and an antacid on postprandial acid delivery into the duodenum in patients with duodenal ulcer. We found that either 400 mg of cimetidine administered with a meal or an ounce of aluminum and magnesium hydroxides, given 1 and 3 hours after the meal, would produce a similar reduction in duodenal acid load during the first four postprandial hours. The results of this study should, of course, be taken only as a guideline since the results are highly dependent on the dosage employed for either agent. However, it provides a reference to help interpret the results of clinical trials.

The study of Peterson et al. (1977) showed that duodenal ulcer in patients on intensive antacid therapy healed at the same rate as observed in patients treated with cimetidine alone. In a subsequent controlled trial, Ippoliti et al. (1978) compared the effect of intensive antacid therapy and cimetidine, finding a similar healing rate of duodenal ulcer for both treatment modalities. However, follow-up studies of patients after the trial had terminated suggest that antacids may be less effective than cimetidine in patients with severe, long-standing duodenal ulcer.

Other considerations besides healing rates are important when deciding whether to use antacids or cimetidine for the treatment of duodenal ulcer. Intensive antacid therapy, employing even well balanced aluminum and magnesium hydroxide combinations, has a high incidence of unpleasant side effects, mostly diarrhea. Cimetidine, in con-



trast, is better tolerated by the majority of patients but, being a systemic drug and relatively new, has potentially unrecognized side effects, which might become apparent as experience with this drug increases. Patient acceptance and compliance are probably greater for cimetidine than for antacids, which require cumbersome liquid administration and a rather rigid schedule. Also, nocturnal acidity is reduced more conveniently by cimetidine than by antacids, which would require frequent administration during the night. Because of these advantages and disadvantages for each therapy, choosing one or the other must remain, for the present time, an individualized decision for the physician and his patient.

Similar comparative data do not exist for anticholinergics versus antacids. Anticholinergics are less potent inhibitors of acid secretion than cimetidine (Richardson et al. 1975). Further, the evidence that anticholinergics alone enhance the healing of peptic ulcer is equivocal (Ivey 1975), even when the drugs are given in a maximally tolerated dose which causes bothersome side effects. However, Feldman et al. (1977) have shown that the acid inhibitory actions of cimetidine and anticholinergics are additive, even when the latter are given at well-tolerated, submaximal doses. The slowing in gastric emptying produced by anticholinergics could potentially improve the efficiency of antacids administered simultaneously.

Despite these encouraging hints, the therapeutic opportunities offered by combinations of available agents are yet to be fully explored. The concept is sound because these drugs have different mechanisms of action and thus their effects may be additive or even synergistic. Thus greater efficacy might be achieved with lower doses and a lesser risk of side effects than if each drug were used independently. Clinical trials should now be designed to test the validity of these assumptions.

#### ADSORBENT PROPERTIES OF ANTACIDS

Antacids, apart from their neutralizing properties, are known to possess adsorbent properties for endogenous secretions such as bile acids or pepsin, certain drugs (Paul & Harrington 1952, Grote & Woods 1953, Chulski & Forist 1958), or bacteria. Bile acid binding by antacids initially reported by

Wenger and Heymsfield (1974) has been recently characterized "in vitro" in our laboratory (Clain et al. 1977). We tested the binding properties of various commercial antacids for the bile acids present in human gallbladder bile obtained at surgery. Aluminum hydroxide was a potent binding agent similar in affinity and capacity to cholestyramine. With aluminum hydroxide, dihydroxy bile acid conjugates were bound more strongly than trihydroxy bile acid conjugates; pH had no effect per se on binding. Magnesium hydroxide and magnesium trisilicate bound bile acids much more weakly. It was also found that aluminum phosphate had a poor bile acid binding capacity. Since ingested aluminum hydroxide is eventually precipitated, at least in part, as aluminum phosphate in the intestine, aluminum hydroxide ingestion may not influence the concentration of bile acids in solution in the small intestinal lumen.

Bile acids produce both functional and structural damage to the gastric mucosa. Reflux of bile into the stomach has been shown to be increased in patients with gastric ulcers, esophagitis, or gastritis, and it is considered to be important in the pathogenesis of these conditions. The finding that aluminum hydroxide is an effective binder of antacids is of potential therapeutic value. Further, bile acids have been shown to be most damaging to the gastric mucosa in the non-ionized state (e.g. at  $\text{pH} < 3$ ) (Eastwood 1975). Use of aluminum hydroxide alone or in combination with cholestyramine would have the additional advantage of raising intragastric pH, which would enhance ionization and, in turn, increase binding. The value of antacids as bile acid binding deserves further investigation "in vivo".

Binding of pepsin by antacids, on the other hand, is of unclear significance since the amounts bound are small relative to the quantities of the enzyme secreted. Binding of drugs is relevant in that bioavailability of medications given concomitantly with antacids may be diminished.

#### PANCREATIC, BILIARY, AND INTESTINAL EFFECTS OF ANTACIDS

Calcium and magnesium ions, present in many antacids, have intestinal effects. Calcium is a pow-

erful stimulant of cholecystokinin (CCK) release, causing pancreatic enzyme secretion and gallbladder contraction (Holtermüller et al. 1976). Magnesium shares some of these stimulatory properties of calcium but it is less potent (Malagelada et al. 1978). On the other hand, magnesium, a poorly absorbed ion, inhibits water and electrolyte secretion from the intestine and at higher concentration induces water secretion. Thus, diarrhea frequently develops after the ingestion of magnesium salts. The mechanism responsible for the intestinal effects of magnesium is poorly characterized. It appears to be, in some aspects, dissociated from the effects on pancreas and gallbladder, because  $MgSO_4$  causes much greater net luminal accumulation of fluid than  $MgCl_2$  (as opposed to similar stimulatory potency of both magnesium salts on the pancreas and gallbladder when infused in equimolar amounts). Thus, the intestinal secretory effect appears to be at least in part "osmotic" and based on sodium diffusion gradients: poorly absorbable ions ( $Mg^{2+}$ ,  $SO_4^{2-}$ ) replacing intraluminal sodium and causing net water transport into the lumen (Fordtran et al. 1968, Potyk 1970). However, it is also possible that magnesium directly stimulates secretion and motility of the gut (Wanitschke & Ammon 1976). In contrast, trivalent aluminum inhibits gastrointestinal motility (Hava & Hurwitz 1973) and aluminum-containing antacids have a delaying effect on bowel transit. The pathogenesis of the effects of these compounds on the gut is poorly understood and clearly deserves further investigation.

#### SIDE EFFECTS AND COMPLICATIONS OF ANTACID THERAPY

The most frequent side effects of antacids are alterations in bowel movement pattern, particularly when ingested in large doses. We have already alluded to the laxative action of magnesium-containing antacids and to the constipating effect of those incorporating aluminum. Combinations of magnesium and aluminum hydroxides are employed in many commercial preparations to offset the opposite effects of each of these compounds on bowel habit.

The milk-alkali syndrome (hypercalcemia, al-

kalosis, and elevated serum creatinine) may develop in patients ingesting large quantities of sodium bicarbonate, calcium carbonate, milk, or combinations of all of these. However, the syndrome has become distinctly less frequent since magnesium and aluminum hydroxide gels are increasingly prescribed for long-term therapy, and milk is less enthusiastically recommended as a panacea to ulcer patients.

Phosphorus depletion due to binding by aluminum salts remains largely a theoretical possibility, because most diets are rich enough in phosphorus to make it unlikely (Robitscher 1968). Absorption of small quantities of magnesium and, to a lesser extent, aluminum is known to occur but may become clinically significant only in patients with advanced renal insufficiency in whom it has been implicated without strong proof in the syndrome of "dialysis prevention". The binding properties of aluminum hydroxide may interfere with the absorption of tetracycline, warfarin, digoxins, quinidine, and other drugs, reducing their bioavailability (Paul & Harrington 1952, Grote & Woods 1953, Chulski & Forist 1958). The slight elevation in blood pH resulting from chronic use of many antacids may increase blood levels of quinidine and aspirin by decreasing their renal excretion.

Many commercial preparations containing amphoteric gels such as aluminum and magnesium hydroxides, as well as sodium bicarbonate, contain enough sodium to preclude their unrestricted use in patients susceptible to sodium overload. Some commercial preparations are explicitly labelled as low in sodium and should be used in these patients, even at the expense of some loss in acid neutralizing power. Intestinal obstruction from impacted antacid has been reported (Potyk 1970).

Antacids are over-the-counter drugs which can and will continue to be used rather freely by patients. The probability that this self-medication with modern antacid preparations causes harmful effects is quite small. Therefore, there seems to be little basis for opposing such practice, which provides gratifying symptomatic relief to many patients.

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## DISCUSSION

*Arnold Berstad:*

Thank you very much for this excellent review. I am sure that there are many questions.

*Flemming Stadil:*

I didn't quite get how you were able to measure the various parameters. Could you explain your techniques?

*Juan-R Malagelada:*

Our method is based on dye-dilution principles. However, because of the presence of food in the stomach we employ mostly radioactive markers or polyethylene glycol, which are easier to measure. Patients are intubated with two tubes: a gastric tube and a two-lumen duodenal tube. The tip of the gastric tube is located in the antrum. The perfusion site of the duodenal tube is placed at the level of the papilla of Vater and the aspiration site, 20 cm distally.

Two markers are used: one is perfused continuously into the second duodenal portion and the other is incorporated into the meal. In our antacid studies a third marker was used, the aluminium present in the antacid mixture, which was measured by absorption spectrophotometry. The principle of this method is that a steady-state perfusion system in the duodenum, with a nonobservable marker, allows estimation of intraluminal flow and passage of any other substance which mixes with it. Thus, it can be determined at any interval how much of the meal marker has passed through the duodenum and, therefore, emptied from the stomach. Knowing how much marker will eventually pass through the duodenum and how much has already passed, at any given time after the meal, it is possible to determine how much of the marker still remains in the stomach. The dilution factor of this gastric marker represents the intragastric volume and the fraction of intragastric volume which leaves with any amount of marker, the gastric emptying rate.

These principles are quite similar to those on which Dr Johansson, Lagerlöf and others at the Karolinska have based their own method. The

aluminium, which is part of the antacid, behaves as a third marker since it is essentially neither secreted nor absorbed. By measuring aluminium passage through the duodenum we can estimate emptying of the antacid. The real difficulty of this method arises when trying to determine the amount of antacid that has reacted with gastric acid. We have approached this by acidifying gastric samples to less than pH 2.0 and then re-titrating them to the original pH. This is complex and time-consuming but, taking into account the amount of antacid present in samples (from aluminium determinations), it provides an estimate of how much antacid in the stomach has not yet reacted with gastric acid.

*Flemming Stadil:*

What about variations in pancreatic secretion - will they have any influence?

*Juan-R Malagelada:*

Absolutely. Pancreatic and biliary secretion should not influence the measurements of intraduodenal flow which are based on dye-dilution principles as explained before. However, some challenge to these techniques comes from the problem of steady-state versus non-steady-state conditions. We all know that under physiological conditions intraluminal steady state is sometimes disturbed, for instance, by rapid gastric emptying, gallbladder discharge, etc. This may also result in poor intraluminal mixing. My own view is that these conditions of extreme disequilibrium introduce some error but the error is usually small. We have attempted to estimate the accuracy of our technique by comparing calculated vs real intragastric volumes, and we find good agreement. It is one of these situations where the theoretical anticipated problems become, in practice, relatively negligible. Catja Johansson and her group have employed not one marker but three markers sequentially perfused into the duodenum to correct for variations in transit time, which become more important when the aspiration point is located further distally in the small bowel. All methods have inherent problems but the principles on which these dilution techniques are based are sound, and substantial information has been ob-

tained by their application by several groups of investigators around the world.

*Arnold Berstad:*

It is not so complicated when you can sit at home and calculate. More questions?

*Hermod Petersen:*

You have tried to answer what happens during a meal and your approach comes closer to physiological than anyone else's, but when you have to eat a meal with a tube put down you are still far from physiological conditions. Some years ago Dr Berstad and I examined the effect of a duodenal tube on acid and pepsin secretion. We found that after 1-2 hours there was a considerable stimulation of gastric secretion, which varied very much from person to person. The effect was independent of whether or not we collected anything from the duodenum. A tube passing the pylorus undoubtedly has some effects.

*Juan-R Malagelada:*

Your point is well taken. We recognize this as a limitation and that is why, when we investigate a problem, we always have a control group. When we compare, let us say, a drug with placebo or one pathological situation to another, we make the assumption that whichever effects may result from intubation or the experimental situation they will occur in both groups. Further, about 2-3 years ago we examined one point that worried us very much. That is: does a transpyloric tube affect postprandial gastric emptying and secretion? We performed these studies by comparing, in the same subject, the emptying of a meal by the Hunt aspiration technique with a duodenal tube in place or withdrawn into the stomach. We did not find any differences. That doesn't mean that there are none; it means that differences in any case are so small as to fall within the experimental error of our method and are therefore unlikely to account for the effects measured when the duodenal tube is in place.

*Flemming Stadil:*

A short question. What about reflux?

*Juan-R Malagelada:*

Reflux in normal individuals or patients with duodenal ulcer, when a meal is present in the stomach, is very small, in the order of 10 % or less of the perfused duodenal marker. Naturally, under certain pathological conditions, it could be much higher.

*Einar Krag:*

I would like to ask you to elaborate a little further on the additional effects of the antacids. I have two questions. First I think the question of the bile acid-binding capacity of the aluminium hydroxide is very interesting and I would like to hear your opinion: do you think it is a more pertinent compound to use for bile acid-induced diarrhoea than cholestyramine? As far as I understood, aluminium hydroxide binds especially the dihydroxy components of the bile acids. Secondly: you said that patients didn't like taking antacids mainly or partly because of the cathartic effect. As far as I understood, the cathartic effect only applies to magnesium-containing preparations. Is that correct?

*Juan-R Malagelada:*

Most antacids consumed in the United States probably contain magnesium in one form or another. There are data available on how often therapy with magnesium-containing antacid causes diarrhoea. For instance, in the study by Peterson et al. (1977) which I quoted in my lecture, about two-thirds of the patients experienced mild diarrhoea at some time during the study. However, these patients were given 2 ounces of liquid antacid after each meal and 1 ounce before retiring. This is a large quantity of antacid but, if less were ingested, the reported high healing rates might not have been achieved.

Regarding your first question about the bile acid-binding capacity, the answer is that I am not sure. Aluminium hydroxide is converted in part to aluminium phosphate in the intestine and remember that aluminium phosphate doesn't have a bile acid-binding capacity. That means that if your aim is to bind soluble gastric bile acids to remove them from contact with the mucosa, then

aluminium hydroxide has a potential. But if what you are trying to accomplish is to increase fecal bile acid losses, then I am not sure that aluminium hydroxide would work because once it is converted to aluminium phosphate in the gut, bound bile acids should again be released into solution.

*Arnold Berstad:*

Do you have any idea about how important this bile acid-binding property may be in the clinical situation? Sometimes I have seen patients with a lot of bile in the stomach, gastritis and low acid secretion. In spite of the low acid they apparently react well to antacids.

*Juan-R Malagelada:*

Our "in-vitro" studies on bile acid-binding by antacids were performed on the stimulus of a potential therapeutic application. The problem is that we really don't know whether bile acids are of pathogenetic importance. If we assume they are, then the most rational approach would be to combine aluminium hydroxide and cholestyramine to take advantage of their somewhat different specificities. The problem is that both are constipating agents. Adding magnesium hydroxide to counterbalance the constipating effect might reduce the bile acid-binding capacity of aluminium hydroxide, based on "in-vitro" data. Perhaps aluminium and magnesium hydroxides could be administered at different times. Recently we have performed some "in-vivo" studies which confirm the bile acid-binding results obtained "in vitro". However, whether it does any good to the patient, I don't know.

*Gerhard Dotevall:*

Talking about the future, you said there is a need for an antacid which retards gastric emptying. Of course this could be done by combining antacids with anticholinergics. I wonder if you have done any studies with your elegant technique on the effect of antacids in combination with anticholinergics?

*Juan-R Malagelada:*

No, we have not. One of the reasons is that such

studies were performed several years ago by Dr Fordtran's group and they found no increase or prolongation of effect of calcium carbonate by adding an anticholinergic drug. I think it was glycopyrrolate.

*Gerhard Dotevall:*

I think Dr Walan will mention another study involving combination of anticholinergics and antacids.

*Anders Walan:*

I am going to comment on all three studies mentioned a little later. But I would like to ask you a question, Dr Malagelada. You found that antacids increased the gastric content. Have you investigated how and why antacids increase the gastric content? Is it due to the neutralization per se or to a specific component of the antacid? If so, is it due to magnesium or aluminium? We have earlier - last year - learnt that aluminium has a specific effect on gastric emptying. I wonder if you have studied any other antacids?

*Juan-R Malagelada:*

The only other antacid we have studied is bicarbonate in patients with chronic pancreatitis. Bicarbonate, like aluminium and magnesium hydroxides, in patients with peptic ulcer disease, produced an increase in gastric secretory output. I suspect this is due to reduced feedback inhibition of gastric secretion produced by increasing the intragastric pH. But it also could be a component of the antacid. We have not studied this ourselves but other investigators have examined, for instance, the effect of magnesium on gastric acid secretion.

*Arnold Berstad:*

Could it simply be so that aluminium hydroxide adheres to the surface of the gastric mucosa?

*Juan-R Malagelada:*

You mean the added volume of the antacid itself?

*Arnold Berstad:*

Adherence to the surface of the mucosa, thereby prolonging the effect of antacids and also increasing the volume of the gastric content.

*Juan-R Malagelada:*

I suppose this could be a reason for slow emptying of the antacid, but I do not think it was responsible for the increase in intragastric volume. The volume of antacid ingested, let us say 60 ml in 4 hours, is very small in comparison with the increase in gastric secretory rate observed. The mechanism of action, as Dr Walan alluded to, is not precisely known. We assume that it is mostly an effect of pH because, for instance, others have shown with intragastric titration that acid output in response to an intragastric stimulus is a function of the intragastric pH.

*Anders Walan:*

Several studies have been published during the last few years on the effect of various components of ordinary antacids. They have mainly focused on the effect on gastric secretion, however, and not on gastric emptying or content. This is so, for example, in the studies by Barreras and also those by Holtermüller. They found an increase after magnesium also but it was not as marked as with calcium.

*Arnold Berstad:*

Have you compared the calcium carbonate preparation and Maalox with respect to the duodenal acid load?

*Juan-R Malagelada:*

We have not done this. Calcium carbonate has been studied rather exhaustively by other investigators in the past. The only thing that we could be adding would be quantification of the duodenal acid load. This might be of interest but calcium carbonate is on its way to disappearing from commercial antacid preparations in the USA and we did not feel compelled to include it in our studies.

*Arnold Berstad:*

Do you agree that calcium carbonate should not be used because of the rebound phenomenon?

*Juan-R Malagelada:*

Maybe, in practical terms, acid rebound is not that significant after all, because it could be abolished by frequent doses of the antacid. On the other hand, by abandoning calcium carbonate, we are losing an antacid of high neutralizing power. My understanding is that, in Europe, calcium carbonate is still very much in use. Is that correct?

*Hermod Petersen:*

I would like to disagree a little with what you said about the future. Cimetidine and antacids have about the same effect on gastric acidity, pH and on the duodenal acid load and it also looks today as if the ulcer-healing effect is the same. You said that the use of antacids is therefore probably going to decrease. You assume that what you have achieved with these large doses of antacids or the doses of cimetidine is a maximal effect on ulcer healing. We don't know anything about this. However, I personally feel convinced that these drugs,  $H_2$ -antagonists, anticholinergics and antacids should be combined. I believe it is important that when an ulcer is present the pH in the stomach and in the duodenum should be above 6 24 hours a day. An ulcer in the stomach or the duodenum will then heal just as rapidly as an ulcer on my finger. Shouldn't we combine these drugs?

*Juan-R Malagelada:*

Combining agents with different mechanisms of action makes sense, of course. Although we have no good clinical data on the effectivity of cimetidine and antacids combined, there is a good basis for it. Cimetidine inhibits acid secretion and therefore it would abolish the increase in gastric secretion that results from acid-neutralization by antacids. At the same time, the latter would neutralize any acid in the stomach which had been secreted in spite of cimetidine. I don't see how these two therapies could be anything less than complementary. However, what I was trying to



imply is that patients often complain when they are asked to take antacids in large amounts and with regularity cimetidine has a greater patient acceptance.

*Arnold Berstad:*

Why is the effect of Maalox more prolonged than the effect of sodium bicarbonate?

*Juan-R Malagelada:*

I think that is because Maalox, at least in gel form, reacts more slowly with acid. With bicarbonate you have almost immediate reaction, which raises the pH up to 6 or 7. By then all the bicarbonate may have been consumed, new acid is secreted by the stomach and there is no antacid left to react with it. Maalox does not raise the pH so high but it lasts longer.

*Arnold Berstad:*

I thought you said that the reaction rate was not important. The critical point was the gastric emptying.

*Juan-R Malagelada:*

It is. But in the case of the bicarbonate the reaction rate is so rapid that you almost give no chance to the gastric emptying to make a difference. When utilizing one of the more slowly reacting gels like aluminium and magnesium hydroxides gastric emptying becomes more important. As I showed earlier, some of the antacid leaves the stomach before it has a chance to react with the gastric acid. Theoretically, we could increase their utilization efficiency from 70-80 % to 100 % if all the antacids stayed in the stomach until they had completely reacted with acid.

*Gerhard Dotevall:*

I think we will hear about long-term treatment with cimetidine this afternoon. But what about long-term treatment of peptic ulcer with antacids and the safety of long-term treatment? Do you have any comments about that?

*Juan-R Malagelada:*

Recent studies on antacids, that I'm aware of, have not been long-term studies in the sense that they have not lasted for several years, as might be required for a disease with prolonged natural history. With regard to complications, there are several to keep in mind, at least theoretically. One that has been mentioned repeatedly in the USA is phosphate depletion in patients ingesting aluminium hydroxide. However, in practice, this is not a problem because there is plenty of dietary phosphate. Fordtran has suggested to give aluminium phosphate supplements to patients on long-term aluminium hydroxide. This is reasonable but whether it is really needed remains doubtful.

*George Sachs:*

Sorry I came in late, but can I give three comments relating to the questions I have heard? I gathered people consider that within the stomach the action of cimetidine or antacids on the pH profile in the lumen might be very similar. I don't think that is correct. Antacids, even if you take the pH up inside the gastric lumen to 8 or 9, will not change the pH of the gastric tubule, due to diffusion striction and solvent flow out through the gastric tubule. Cimetidine, of course, will lower the pH down to neutrality if there is complete block. Secondly, in terms of the volume flow that antacids induce, I think a simple explanation is the isotonic obligation induced by addition of sodium chloride or aluminium chloride or calcium chloride to the gastric contents.

*Juan-R Malagelada:*

If we consider gastric ulcer, your comment would certainly be appropriate. If we are talking about duodenal ulcer, then it would not be because acid has to leave the stomach to reach the lesion. About the osmolality, I agree, this could be a factor.

*Anders Walan:*

I wonder if it matters even if it is a gastric ulcer, because the gastric ulcer is almost never in the fundic region, where acid is secreted. You men-

tioned long-term studies. There is at least one long-term study I am aware of and that is by Cayer et al. (1957). They gave 4 antacid tablets or placebo 2 hours after each meal and at night for 8 1/2 months and 74 % of the patients who took antacids were free from pain compared to 24 % in the placebo group. I have not seen any other long-term studies.

*Juan-R Malagelada:*

I do remember that study but they did not verify ulcer healing, they looked at symptoms. Is that right?

*Anders Walan:*

They looked at the symptomatic recurrence and this was also significantly lower in patients taking antacids. They did not look at ulcer healing. It was a long-term study. With bicarbonate you sometimes can come up to very high pH levels. What about the observation made by Grossman et al. this year that if you have amino acids in the stomach and then bring the pH up to very high levels, 9 or perhaps 10, you will have a pronounced increase in acid secretion which is not even inhibited by cimetidine. How do you explain that?

*Juan-R Malagelada:*

I think Dr Sachs would like to answer.

*George Sachs:*

Can I make a comment to the Grossman experiment? There is an artefact because they used intragastric titration or back titration starting at pH 8 or 9. This is an amino-acid mixture and the majority of what they were titrating was CO<sub>2</sub> diffusion into the lumen. It was not acid secretion.

*Juan-R Malagelada:*

I agree with Dr Sachs.

*Arnold Berstad:*

Concerning the future, we have an antacid named Novalucol or Balancid® and we are very satisfied with it. It is very potent, more potent than Maalox, and the effect is rather prolonged. How might it be made better? Is it possible?

*Juan-R Malagelada:*

What is the composition of this product?

*Gunnar Ekenved:*

Novalucol forte, or Balancid® contains the same active substances as Maalox – aluminium and magnesium hydroxides – but it has about double acid-binding capacity – 52.5 mmol/10 ml. Thus Novalucol forte has an acid-binding capacity which is higher than any other antacid product, including calcium carbonate suspensions.

*Juan-R Malagelada:*

Yes, and calcium carbonate is very convenient for patients to take in the form of tablets which dissolves rapidly in the stomach. Calcium carbonate is a good antacid, if it were not for its acid rebound effect. Don't you agree?

*Gunnar Ekenved:*

Yes, I do. I also think that antacids should be rated according to their acid-binding capacity. We have found that it is possible to formulate tablets of aluminium hydroxide and magnesium hydroxide compounds with as good acid-binding capacity as calcium carbonate tablets.

*Juan-R Malagelada:*

In our studies we have only examined the effect of one antacid, aluminium and magnesium hydroxides, so I cannot provide any comparative data with other antacids. However, I think that if new products were developed, it might be useful to employ methods such as ours to evaluate them under physiological conditions.

*Arnold Berstad:*

From the point of view of the compliance of the patients, it is important that the volume of antacids is kept low. How much Balancid® is equivalent to 30 ml of Maalox, used in several different studies in the United States?

*Gunnar Ekenved:*

30 ml of Maalox corresponds to 15 ml of Balancid® or Novalucol forte.

*Juan-R Malagelada:*

Yes, this would be an advantage, because patients often complain about having to go around with big bottles of antacid.

*Sven Moberg:*

Do you think that it is possible to increase the effect of antacids by combining them with fatty acids, since fatty acids inhibit gastric emptying? Furthermore, fatty acids increase the retroperistaltic motility within the duodenum, which also may increase the neutralizing effect of duodenal content within the bulb.

*Juan-R Malagelada:*

I suppose one might object at adding a high calorie-producing nutrient to an antacid which is to be consumed around the clock. Wouldn't you think so?

*Sven Moberg:*

Well, I don't think you need such big amounts of fatty acids, but I have no figures in mind at present.

*Juan-R Malagelada:*

It would probably be the same thing as if the patient ate a meal rich in fat, which would slow gastric emptying, and took the antacid afterwards.

*Sven Moberg:*

Especially when you take the antacid dose 3 hours after a meal, it could well contain fatty acids.

*Juan-R Malagelada:*

One of the definite advantages of cimetidine is that it has a prolonged action. Antacids taken at bedtime probably have a short-lasting effect and the patient remains unprotected for most of the night, whereas with cimetidine prolonged inhibition of acid secretion can be achieved.

*Arnold Berstad:*

The last question to Dr Walan.

*Anders Walan:*

A very short comment on this last issue. I think it would cause big problems to the pharmacies because if the fatty acid were a polyunsaturated fatty acid it would change very rapidly with time. It would not taste very good after some months.

*Juan-R Malagelada:*

Perhaps we should continue to search for ways of slowing gastric emptying and prolonging the effect of antacids. However, you will have noticed from our studies that antacid efficiency was usually of the order of 70-80 %. Therefore, we can expect only a marginal gain, but worth achieving if we can.

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# COMPARISON OF AN $H_2$ RECEPTOR ANTAGONIST AND A NEUTRALIZING ANTACID ON POSTPRANDIAL ACID DELIVERY INTO THE DUODENUM IN PATIENTS WITH DUODENAL ULCER

TIMOTHY B. DEERING, M.D., AND JUAN-R. MALAGELADA, M.D.

*Gastroenterology Unit, Mayo Clinic and Mayo Foundation, Rochester, Minnesota*

Measurement of the postprandial rate of acid delivery into the duodenum directly assessed the efficacy of two radically different acid-reducing therapies for duodenal ulcer disease. Cimetidine, 400 mg, with an ordinary solid meal decreased the 4-hr delivery of titratable acid and hydrogen ion into the duodenum by 63 and 86%, respectively ( $P < 0.01$  versus control). Liquid Maalox, 30 ml, 1 and 3 hr after an identical meal reduced 4-hr delivery of acid by 47 and 74%, respectively ( $P < 0.01$  versus control). During the study period, the  $H_2$  receptor antagonist effected a continuous reduction in gastric acidity and the delivery of acid into the duodenum. The liquid neutralizing antacid produced a more fluctuating decrease in these parameters. However, given in these dosages, the magnitude and duration of the acid-reducing effect were similar for both treatments.

Even seasoned skeptics are beginning to accept the possibility that histamine  $H_2$  receptor antagonists will revolutionize the therapy of peptic ulcer disease. If so, will  $H_2$  antagonists replace liquid neutralizing antacids in the standard ulcer regimen? We have compared the effect of these two radically different drugs on the postprandial delivery of acid into the duodenum of patients with duodenal ulcer, under experimental circumstances closely resembling physiological conditions. This has been made possible by recently developed methodology<sup>1</sup> that allows accurate quantification of gastric emptying of acid as well as other gastric functions after the ingestion of an ordinary solid-liquid meal. During the postprandial period, the stomach acts in part as a reservoir and therefore the rate of acid secretion does not necessarily equal the rate of acid delivery into the duodenum. Presumably the latter is more directly related to the pathogenesis of duodenal ulcer. In our studies, the hydrogen ion and titratable acid entering the duodenum were quantified, since both parameters were considered relevant to the interpretation of our observations.

We designed the study using dosages that would be realistic in clinical practice. From our experience with the use of cimetidine in doses of 200 and 300 mg taken with a similar meal,<sup>2</sup> it appeared that a dose of 400 mg

would be necessary to achieve substantial suppression of acid secretion and still remain within the limits of prior pharmacological testing.<sup>3</sup> Administration of the dose at the beginning of the meal is the simplest way of achieving patient compliance. For the neutralizing antacid, we chose a magnesium and aluminum hydroxide mixture, Maalox, because it is commonly used by patients, has high neutralizing capacity,<sup>4</sup> and does not contain calcium carbonate. The optimum schedule for using antacid is in the postprandial period,<sup>3</sup> 1 and 3 hr after each meal. Patient compliance in using liquid antacid is generally poor,<sup>5</sup> and dosages greater than 30 ml twice after each meal are not likely to be acceptable to patients because of the resulting diarrhea and poor palatability.

## Methods

Eighteen studies were performed in 6 patients with current symptoms and radiological evidence of duodenal ulcer. This investigation was approved by the Mayo Clinic Human Studies Committee, and each patient consented in writing to participate. The 5 men and 1 woman, 23 to 63 years of age, had no previous gastrointestinal or biliary tract surgery and no evidence of gastric outlet obstruction. Scheduled in random order, each patient took 400 mg of cimetidine at the beginning of the meal on 1 day, 30 ml of Maalox 1 and 3 hr after the meal on a 2nd day, and no treatment on a 3rd day.

The intubation and perfusion methods have been described previously in detail.<sup>1</sup> Briefly, beginning at 7:00 A.M., a triple lumen duodenal tube was positioned fluoroscopically with a perfusion site at the level of the ampulla of Vater and an aspiration site 20 cm distally at the angle of Treitz. A size 16 Salem sump tube was positioned fluoroscopically in the antrum. The duodenum was perfused continuously at 2 ml per min with a solution of 0.9% saline and 0.5  $\mu$ Ci per liter of [ $^{14}$ C]polyethylene glycol (PEG). The stomach was initially emptied by aspiration and then three 10-min basal collections were obtained by continuous suction ( $-50$  mm Hg) assisted by intermittent manual aspiration.

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Address requests for reprints to: Dr. Juan-R. Malagelada, Gastroenterology Unit, Mayo Clinic, Rochester, Minnesota 55901.

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The standard meal<sup>1</sup> consisted of 90 g (uncooked weight) of tenderloin steak, coarsely ground to facilitate chewing, cooked, and seasoned with 0.1 g of salt; 25 g of white bread with 8 g of butter; and 60 g of vanilla ice cream topped with 35 g of chocolate syrup. A glass of water (240 ml) taken with the meal contained 15 g of PEG 4000. The total caloric value of the meal was 458 calories distributed approximately as 40% carbohydrate, 40% fat, and 20% protein. After blenderizing, the measured volume, osmolality, and pH of the meal were 400 ml, 540 milliosmoles, and 6.0, respectively.

Gastric suction was discontinued, and the patient then ate the meal and drank the marker within 20 min. Gastric (10 ml) and duodenal samples were collected thereafter at 10-min intervals as described before<sup>1</sup> for the next 5 hr. At 1/2, 1, 2, 3, 4, and 5 hr, blood samples were obtained for measurement of cimetidine levels.

In the gastric samples we immediately measured the pH with a calibrated<sup>7</sup> Fisher model 250 digital pH meter, and the glass electrode readings were converted to hydrogen ion activity.<sup>7</sup> Samples were also titrated to pH 6.0 (pH of the meal) with the use of 0.05 N NaOH. PEG 4000 and [<sup>14</sup>C]PEG concentration in the gastric and duodenal aspirates were measured as previously described.<sup>1</sup> Cimetidine concentration was analyzed by high pressure liquid chromatography (Biochemistry Department, Smith Kline and French Laboratories).

For calculation of the postprandial total acid content of the stomach and the rates of acid (titratable acid and hydrogen ion) delivery into the duodenum, we used the equations previously described in detail.<sup>1</sup> We have used the hydrogen ion activity (as determined by the glass pH electrode) as the closest estimation of hydrogen ion concentration in order to calculate the amount of dissociated hydrogen ion entering the duodenum. No attempt was made to convert hydrogen ion activity to hydrogen ion concentration, using Moore's reciprocity tables<sup>8</sup> since they may only be valid for fasting gastric juice and not for postprandial gastric contents. For the titratable acid and the hydrogen ion, the significance of the differences between treatments was determined by the paired *t*-test. The significance of the pH differences between the treatments was determined by the binomial sign test since pH is a logarithmic parameter.<sup>9</sup>

## Results

**Intragastric pH.** On all 3 days, the peak gastric pH occurred at 20 min when the first samples were obtained. Almost constantly beyond the 1st hr, the intragastric pH was significantly higher with both treatments than after the control meal alone. Although the postprandial intragastric pH tended to fluctuate more with Maalox, only sporadic significant differences occurred between the Maalox and cimetidine treatments and these were not consistently in favor of either one (fig. 1).

**Titratable acid contained in the stomach and emptied into the duodenum.** These parameters represent the total amount of acid present in the stomach at any given time during the postprandial period and the portion of the total acid delivered into the duodenum, respectively. Titratable acid is not affected by the presence of food,<sup>1</sup> and it does not include acid that has already reacted with the neutralizing antacid.

As can be appreciated from figure 2, cimetidine continually reduced the total postprandial acid content of the stomach whereas Maalox achieved a comparable effect only during the hour following each dose. How-

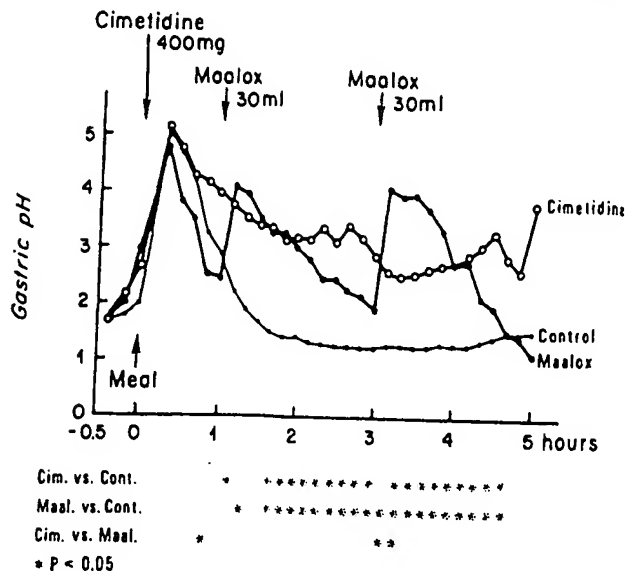


FIG. 1. Effect of therapy on intragastric pH after ingesting a meal at 0 hr. Cimetidine (400 mg) was taken at onset of meal on 1 day. Liquid Maalox (30 ml) was taken 1 and 3 hr after onset of meal on a 2nd day. No medication was given on control day. Asterisks (\*) indicate significant differences between treatments.

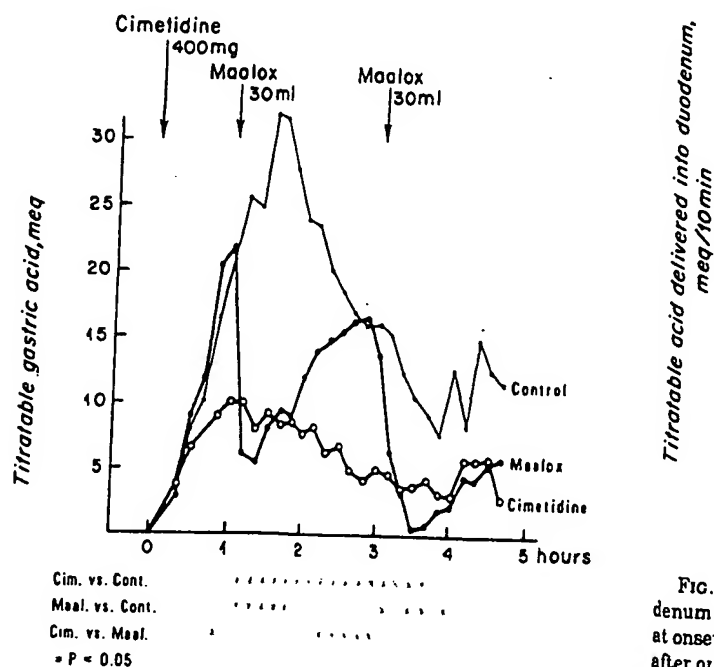


FIG. 2. Effect of therapy on total acid content of the stomach after ingesting a meal at 0 hr. Cimetidine (400 mg) was taken at onset of meal on 1 day. Liquid Maalox (30 ml) was taken 1 and 3 hr after onset of meal on a 2nd day. No medication was given on control day. Asterisks (\*) indicate significant differences between treatments.

ever, the superior effect of cimetidine was partially mitigated because the stomach delayed the delivery of acid into the duodenum during the 2nd hour after Maalox. The next dose of Maalox then reversed in part the acid accumulation in the stomach that occurred between

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the two doses (fig. 3). The total titratable acid emptied during the first 4 hr after the meal was not significantly different between cimetidine and Maalox (table 1).

**Hydrogen ion delivered into the duodenum.** The postprandial rate of hydrogen ion delivery into the duodenum on the control day increased rapidly during the 1st hr and plateaued for the next 2 to 3 hrs. Cimetidine and Maalox therapy significantly reduced the hydrogen ion entering the duodenum for most periods after the 1st hr, except for 20 to 30 min near the 3rd hr. No significant differences were noted between the treatments, except during the 4th postprandial hr, when Maalox was statistically more effective during one 10-min period (fig. 4). The total amount of hydrogen ion emptied into duodenum during the 4 hr postprandial period did not differ between the two treatments (table 1).

**Blood cimetidine levels.** The mean  $\pm$  SEM cimetidine blood levels were  $0.34 \pm 0.07$   $\mu$ g per ml at 1/2 hr,  $1.38 \pm 0.05$   $\mu$ g per ml at 1 hr,  $1.15 \pm 0.10$   $\mu$ g per ml at 2 hr,  $0.99 \pm 0.04$   $\mu$ g per ml at 3 hr,  $0.54 \pm 0.09$   $\mu$ g per ml at 4 hr, and  $0.49 \pm 0.12$   $\mu$ g per ml at 5 hr. The peak cimetidine blood levels (mean  $\pm$  SEM) measured in similar studies<sup>2</sup> using 200- and 300-mg dosages were  $0.6 \pm 0.9$  and  $1.0 \pm 0.1$ , respectively, at 1 hr.

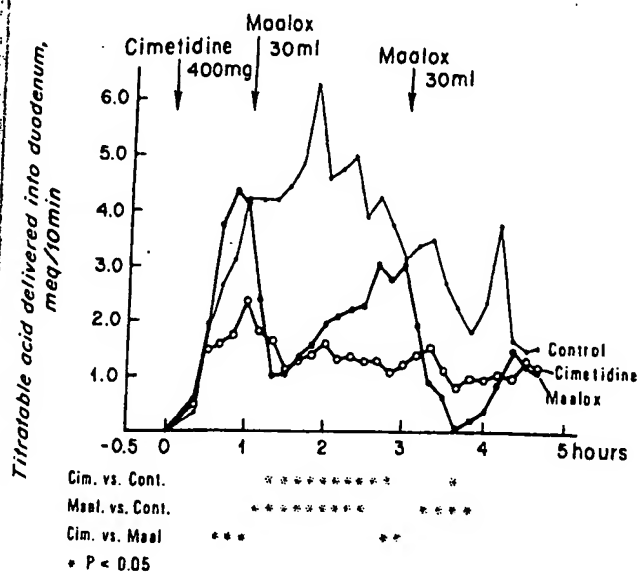


FIG. 3. Effect of therapy on delivery of titratable acid into duodenum after ingesting a meal at 0 hr. Cimetidine (400 mg) was taken at onset of meal on 1 day. Liquid Maalox (30 ml) was taken 1 and 3 hr after onset of meal on a 2nd day. No medication was given on control day. Asterisks (\*) indicate significant differences between treatments.

TABLE 1. Four-hour postprandial delivery of acid into duodenum

|                    | Control        | Cimetidine                       | Maalox                            |
|--------------------|----------------|----------------------------------|-----------------------------------|
| MEQ $\pm$ SEM/4 hr |                |                                  |                                   |
| Titratable acid    | 80.7 $\pm$ 7.2 | 30.0 $\pm$ 7.7 <sup>a</sup> (63) | 42.4 $\pm$ 10.8 <sup>a</sup> (47) |
| Hydrogen ion       | 32.6 $\pm$ 4.4 | 4.5 $\pm$ 1.7 <sup>a</sup> (86)  | 8.4 $\pm$ 3.8 <sup>a</sup> (74)   |

<sup>a</sup>  $P < 0.01$ , treatment versus control; numbers in parentheses represent percentage of reduction from control value.

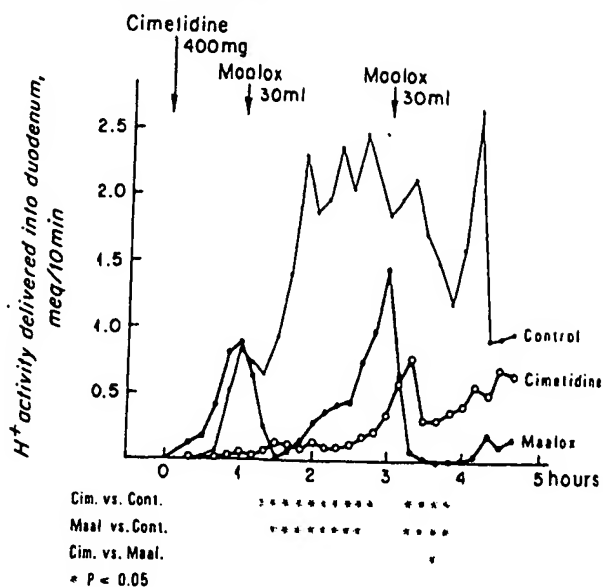


FIG. 4. Effect of therapy on delivery of hydrogen ion into duodenum after ingesting a meal at 0 hr. Cimetidine (400 mg) was taken at onset of meal on 1 day. Liquid Maalox (30 ml) was taken 1 and 3 hr after onset of meal on a 2nd day. No medication was given on control day. Asterisks (\*) indicate significant differences between treatments.

## Discussion

Most duodenal ulcers reside in the mucosa of the first portion of the duodenum, where they bathe regularly in the acid emptied there from the stomach. A direct way of assessing the efficacy of acid-reducing treatment for duodenal ulcer disease is to measure its effect on acid delivery into the duodenum. In the dosages used, cimetidine and Maalox significantly decreased the rate of emptying of acid—both titratable acid and hydrogen ion—after a meal. However, the magnitude and duration of this effect were similar for both treatments.

Cimetidine and Maalox reduce the acid entering the duodenum by completely different mechanisms. The histamine H<sub>2</sub> receptor antagonist inhibits the secretion of gastric acid.<sup>2, 8-11</sup> In contrast, the aluminum and magnesium hydroxides in the liquid antacid neutralize acid that has already been secreted by the stomach;<sup>4</sup> therefore, the acid delivered into the duodenum is that which remains unneutralized by the antacid. Cimetidine appears to be most effective in the fasting state,<sup>10</sup> and its inhibitory action on nocturnal acid may be marked and prolonged.<sup>10, 12</sup> When a patient eats a meal, acid secretion is stimulated and the effect of cimetidine is diminished.<sup>2</sup> In contrast, food delays gastric emptying and helps to retain the liquid antacid in the stomach<sup>3</sup> and thus prolongs the neutralizing effect, which is relatively slow and is wasted if the antacid leaves the stomach without reacting with acid.<sup>4</sup> Comparison of the total titratable acid and the hydrogen ion delivered into the duodenum after the meal showed that buffering by food (especially protein) reduces the rate of emptying of hydrogen ion into the duodenum—particularly during the early postprandial period. Thus, although the neutraliz-

ing antacid was not given until 1 hr after the meal (when cimetidine would have already been inhibiting acid secretion), the rate of delivery of hydrogen ion into the duodenum remained low during that 1st postprandial hr (even without therapy) because of the large amount of meal still present in the stomach.

The 400-mg dose of cimetidine was more effective than the 300-mg dose used previously in our laboratory.<sup>2</sup> Cimetidine reduced the maximal control 1-hr delivery of titratable acid into the duodenum from  $29.6 \pm 3.3$  to  $8.0 \pm 2.1$  mEq and from  $28.8 \pm 3.8$  to  $14.8 \pm 2.5$  mEq for 400- and 300-mg doses, respectively ( $P < 0.05$ ;  $t$ -test). The peak blood levels were also higher:  $1.38 \pm 0.05$  and  $1.0 \pm 0.1$   $\mu$ g per ml, respectively ( $P < 0.005$ ,  $t$ -test). Despite higher blood levels, the rapid rise in the gastric pH seen with the 300-mg dose during the 4th postprandial hr<sup>2</sup> was not observed in the present 400-mg study, perhaps because we did not resort to constant gastric aspiration in the late postprandial period.

Fordtran and associates observed that the effect of 60 ml of Maalox after a meal persisted for 2 hr, although the authors were able to measure only pH and acid concentration at that time.<sup>4</sup> Figures 3 and 4 show that 30 ml of the antacid given 1 hr after a meal significantly reduced both the titratable acid and the hydrogen ion emptied into the duodenum for almost 2 hr but that the effect then rapidly diminished. A second dose of neutralizing antacid is therefore necessary 3 hr after the meal to continue the reduction of the acid entering the duodenum until the cycle begins again with a new meal.

Patients with duodenal ulcer may readily accept the H<sub>2</sub> antagonists because of their efficacy<sup>13, 14</sup> and convenience; however, long term maintenance therapy<sup>15</sup> may prove expensive, and some patients may not tolerate these new drugs. Our studies suggest that an oral dose of 400 mg of cimetidine is necessary to match the reduction in postprandial duodenal acid load produced by Maalox prescribed 1 and 3 hr after meals. Thus, liquid antacid still provides a rational alternative therapy for duodenal ulcer disease during daytime. On the other hand, antacid stays only briefly in the empty stomach<sup>5</sup> and so would not match the prolonged nocturnal inhibition of gastric acid secretion by cimetidine.<sup>2</sup> In the future, therapy combining liquid neutralizing antacid and

histamine H<sub>2</sub> receptor antagonists may find clinical application in the management of duodenal ulcer disease.

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contained in the monograph. Products which do not meet both of these requirements shall be subject to the requirements for Category I products. If testing is promptly undertaken but data adequate to prove effectiveness are not submitted to the Food and Drug Administration within the 2-year period, the ingredients listed in this category will no longer be permitted, even in a product that meets the in vitro antacid effectiveness standard, because of a lack of evidence that these ingredients make a meaningful contribution to the claimed effect for the product.

1. *Alginic acid*. Although the ingestion of alginic acid-containing products may produce a layer of material floating on top of the gastric contents, the available evidence is insufficient to demonstrate clinical effectiveness. The studies are fragmentary, uncontrolled, and few in number. No evidence is presented as to reproducibility of results. There is insufficient evidence that alginic acid-containing antacid products, even if they do produce a floating layer on top of the gastric contents, are clinically beneficial. Indeed, such evidence as there is indicates that these products do not increase the pH of gastric contents as a whole. Since regurgitation of gastric contents is particularly apt to occur when patients are lying down rather than in the upright position, alginic acid-containing products may be less beneficial than a standard antacid which is more likely to increase the pH throughout the gastric contents.

Alginic acid is safe in amounts usually taken orally (e.g., 4 grams per day) in antacid products.

2. *Attapulgitte (activated)*. This ingredient is safe in the amounts usually taken orally in antacid products.

3. *Charcoal, activated*. Charcoal is presently considered safe in amounts usually taken orally in antacid products, but study is specifically needed to determine whether the charcoal used contains benzpyrene or methylcholanthrene type carcinogens. Since charcoal-containing products may decrease absorption of certain oral drugs, the label shall bear the following drug interaction precaution: "Drug Interaction Precautions: Do not take this product if you are presently taking any prescription drug."

4. *Gastric mucin*. This ingredient is safe in the amounts usually taken orally in antacid products.

5. *Kaolin*. Kaolin is safe in amounts usually taken orally in antacid products. Since kaolin affects gastro-intestinal absorption, kaolin interferes with the absorption of lincomycin, and therefore the label shall bear the following drug interaction precaution: "Drug Interaction Precautions: Do not take this product if you are presently taking a prescription antibiotic drug containing lincomycin."

6. *Methylcellulose*. Methylcellulose is safe in amounts usually taken orally (e.g., 2 grams per day in antacid products).

7. *Pectin*. Pectin is safe in the amounts usually taken orally in antacid products.

8. *Carboxy methylcellulose*. Carboxy methylcellulose is safe in amounts usually taken (e.g., 3 grams per day) in antacid products.

B. *Labeling*. Marketing under the following labeling conditions may continue for a period of 2 years after the date of publication of this determination subject to the same requirements specified above for the use of Category III ingredients.

1. OTC products containing ingredients listed in Category I or III are often used to treat symptoms that are not known to be related to acidity of gastric contents. These products may or may not qualify as antacids by the in vitro acid neutralizing test. The symptoms include "indigestion", "gas", "upper abdominal pressure", "full feeling", "nausea", "excessive eructations", "upset stomach", and the like. Some of these symptoms are vague, most are poorly understood as to pathophysiological mechanism, and none has been shown by adequate and reliable scientific evidence to be caused by or alleviated by changes in gastric acidity.

2. Claims or indications which link certain signs and symptoms, such as "sour breath", "upper abdominal pressure", "full feeling", "nausea", "stomach distress", "indigestion", "upset stomach", and "excessive eructations" with normal or hypernormal gastric acidity, are unproven since the relationship of such signs and symptoms to gastric acidity is unknown or dubious and there is no adequate and reliable scientific evidence to support these claims. Such claims or indications encourage the user to draw conclusions as to the cause or intermediation of such symptoms, a conclusion that even the medical profession is incapable of drawing at this time.

3. The evidence currently available is inadequate to support the claim that such properties as "floating", "coating", "defoaming", "demulcent", and "carminative" contribute to the relief of upper gastrointestinal symptoms. The continued use of such claims, or ones closely allied to them, requires additional studies both to confirm the claimed specific action and to demonstrate clinical significance.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-42 as amended, 1050-53 as amended, 1055-56 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended; 5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to the Commissioner (21 CFR 2.120) and based upon the administrative record in this proceeding, Title 21 of the Code of Federal Regulations is amended by adding Parts 331 and 332 (formerly §§ 130.305 and 130.306) to Subchapter D to read as follows:

| Subpart A—General Provisions |  |
|------------------------------|--|
| Sec. 331.1                   | Scope.   |
| Subpart B—Active Ingredients |  |
| 331.10                       | Antacid active ingredients.                                  |
| 331.11                       | Listing of specific active ingredients.                      |
| 331.15                       | Combination with nonantacid active ingredients.              |
| Subpart C—Testing Procedures |  |
| 331.20                       | Apparatus and reagents.                                      |
| 331.21                       | Determination of percent contribution of active ingredients. |
| 331.22                       | Reagent standardization.                                     |
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| Subpart D—Labeling |                               |
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| 331.30             | Labeling of antacid products. |
| 331.31             | Professional labeling.        |

#### Subpart A—General Provisions

##### § 331.1 Scope.

An over-the-counter antacid product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

#### Subpart B—Active Ingredients

##### § 331.10 Antacid active ingredients.

(a) The active antacid ingredients of the product consist of one or more of the ingredients permitted in § 331.11 within any maximum daily dosage limit established, each ingredient is included at a level that contributes at least 25 percent of the total acid neutralizing capacity of the product, and the finished product contains at least 5 mEq. of acid neutralizing capacity and results in a pH of 3.5 or greater at the end of the initial 10-minute period as measured by the method established in § 331.25. The method established in § 331.21 shall be used to determine the percent contribution of each antacid active ingredient.

(b) This section does not apply to an antacid ingredient specifically added as a corrective to prevent a laxative or constipating effect.

##### § 331.11 Listing of specific active ingredients.

(a) Aluminum-containing active ingredients:

- (1) Aluminum carbonate.
- (2) Aluminum hydroxide (or as aluminum hydroxide-hexitol stabilized polymer, aluminum hydroxide-magnesium carbonate codried gel, aluminum hydroxide-magnesium trisilicate codried gel, aluminum-hydroxide sucrose powder hydrated).

(3) Dihydroxyaluminum aminoacetate and dihydroxyaluminum aminocollid acid.

(4) Aluminum phosphate, maximum daily dosage limit 8 grams.

(5) Dihydroxyaluminum sodium carbonate.

(b) Bicarbonate-containing active ingredients: Bicarbonate ion; maximum



daily dosage limit 200 mEq. for persons up to 60 years old and 100 mEq. for persons 60 years or older.

(c) Bismuth-containing active ingredients:

- (1) Bismuth aluminate.
- (2) Bismuth carbonate.
- (3) Bismuth subcarbonate.
- (4) Bismuth subgallate.
- (5) Bismuth subnitrate.

(d) Calcium-containing active ingredients: Calcium, as carbonate or phosphate; maximum daily dosage limit 160 mEq. calcium (e.g., 8 grams calcium carbonate).

(e) Citrate-containing active ingredients: Citrate ion, as citric acid or salt; maximum daily dosage limit 8 grams.

(f) Glycine (aminoacetic acid).

(g) Magnesium-containing active ingredients:

(1) Hydrate magnesium aluminate activated sulfate.

(2) Magaldrate.

(3) Magnesium aluminosilicates.

(4) Magnesium carbonate.

(5) Magnesium glycinate.

(6) Magnesium hydroxide.

(7) Magnesium oxide.

(8) Magnesium trisilicate.

(h) Milk solids, dried.

(i) Phosphate-containing active ingredients:

(1) Aluminum phosphate; maximum daily dosage limit 8 grams.

(2) Mono or dibasic calcium salt; maximum daily dosage limit 2 grams.

(3) Tricalcium phosphate; maximum daily dosage limit 24 grams.

(j) Potassium-containing active ingredients:

(1) Potassium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older.

(2) Sodium potassium tartrate.

(k) Sodium-containing active ingredients:

(1) Sodium bicarbonate (or carbonate when used as a component of an effervescent preparation); maximum daily dosage limit 200 mEq. of sodium for persons up to 60 years old and 100 mEq. of sodium for persons 60 years or older, and 200 mEq. of bicarbonate ion for persons up to 60 years old and 100 mEq. of bicarbonate ion for persons 60 years or older. The warning required by § 330.1(g) concerning overdoses is not required on a product containing only sodium bicarbonate powder.

(2) Sodium potassium tartrate.

(l) Silicates:

(1) Magnesium aluminosilicates.

(2) Magnesium trisilicate.

(m) Tartarate-containing active ingredients. Tartaric acid or its salts; maximum daily dosage limit 200 mEq. (15 grams) of tartarate.

§ 331.15 Combination with nonantacid active ingredients.

(a) An antacid may contain any generally recognized as safe and effective nonantacid laxative ingredient to cor-

rect for constipation caused by the antacid. No labeling claim of the laxative effect may be used for such a product.

(b) An antacid may contain any generally recognized as safe and effective analgesic ingredient(s), if it is indicated for use solely for the concurrent symptoms involved, e.g., headache and acid indigestion, and is marketed in a form intended for ingestion as a solution.

(c) An antacid may contain any generally recognized as safe and effective antifatulent ingredient if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

#### Subpart C—Testing Procedures

##### § 331.20 Apparatus and reagents.

(a) pH meter, equipped with glass and saturated calomel electrodes.

(b) Magnetic stirrer.

(c) Magnetic stirring bars (about 40 mm. long and 10 mm. in diameter).

(d) 50 ml. buret.

(e) Buret stand.

(f) 100 ml. beakers.

(g) 250 ml. beakers.

(h) 10 ml., 20 ml. and 30 ml. pipets calibrated to deliver.

$$\text{Percent contribution} = \frac{\text{Total mEq. Antacid Active Ingredient} \times 100}{\text{Total mEq. Antacid Product}}$$

##### § 331.22 Reagent standardization.

Standardize the sodium hydroxide (NaOH) and Hydrochloric acid (HCl) solutions according to the procedures in the United States Pharmacopeia XVIII (NaOH page 1036 and HCl page 1034) or the Official Methods of Analysis of the Association of Official Analytical Chemists, 11th Ed., 1970, (NaOH page 876 and HCl page 873).<sup>2</sup>

##### § 331.23 Temperature standardization.

All tests shall be conducted at 25° C ± 3°.

##### § 331.24 Tablet disintegration test.

A tablet disintegration test shall be performed on tablets that are not to be chewed following the procedures described in the United States Pharmacopeia XVIII (page 932). If the label states the tablet may be swallowed, it must disintegrate within a 10-minute time limit pursuant to the test procedure using simulated gastric fluid test solution without enzymes, the United States Pharmacopeia XVIII page 1026, rather than water as the immersion fluid.

##### § 331.25 Preliminary antacid test.

(a) pH meter. Standardize the pH meter at pH 4.0 with the standardizing buffer and check for proper operation at pH 1 with 0.1 N HCl.

(b) Dosage form testing—(1) Liquid sample. Place an accurately weighed

- (i) Tablet comminuting device.
- (j) A number 20 and 100 U.S. standard mesh sieve.
- (k) Tablet disintegration apparatus.
- (l) 0.1 N, 0.5 N and 1.0 N hydrochloric acid.
- (m) 0.5 N sodium hydroxide.
- (n) Standard pH 4.0 buffer solution (0.05 M potassium hydrogen phthalate).
- (o) 95 percent ethanol.
- (p) Distilled Water.

##### § 331.21 Determination of percent contribution of active ingredients.

To determine the percent contribution of an antacid active ingredient, place an accurately weighed amount of the antacid active ingredient equal to the amount present in a unit dose of the product into a 250 ml. beaker. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix thoroughly to wet the sample (ethanol may affect the acid neutralizing capacity). Add water to a volume of 70 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.26 and calculate the percent contribution of the antacid active ingredient in the total product as follows:

(calculate density) and well mixed amount of the antacid product equivalent to the minimum labeled dosage; e.g., 5 ml., into a 100 ml. beaker. Add sufficient water to obtain a total volume of about 40 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. Analyze the sample according to the procedure set forth in § 331.25.

(2) Chewable and non-chewable tablet sample. Place an accurately weighed amount of a tablet composite equivalent to the minimum labeled dosage into a 100 ml. beaker. (The composite shall be prepared by determining the average weight of not less than 20 tablets and then comminuting the tablets sufficiently to pass through a number 20 U.S. standard mesh sieve and held by a number 100 U.S. standard mesh sieve.) Mix the sieved material to obtain a uniform sample. If wetting is desired, add not more than 5 ml. of 95 percent ethanol and mix to wet the sample thoroughly (ethanol may effect the acid neutralizing capacity). Add water to a volume of 40 ml. and mix on magnetic stirrer at 300 ± 30 r.p.m. for about one minute. (Capsules should be tested in the same manner using the sieved capsule powder as the sample.) Analyze the sample according to the procedure set forth in § 331.25.

(3) Effervescent sample. Place an amount equivalent to the minimum labeled dosage into a 100 ml. beaker. Add 10 ml. water and swirl the beaker gently while allowing the reaction to subside. Add another 10 ml. of water and swirl the beaker gently. Wash down the walls of the beaker with 20 ml. of water and

<sup>2</sup> Copies may be obtained from: Association of Official Analytical Chemists, P.O. Box 540, Benjamin Franklin Station, Washington, DC 20044.



per minimum time interval. For compliance purposes, the value determined by the acid neutralizing test at any point in time shall be at least 90 percent of the labeled value. No product shall be marketed with an acid neutralizing capacity below 5 mEq.

(2) May contain an indication for the symptomatic relief of hyperacidity associated with the diagnosis of peptic ulcer, gastritis, peptic esophagitis, gastric hyperacidity, and hiatal hernia.

(b) Professional labeling for an anti-acid-antiflatulent combination may contain the information allowed for health professionals for antacids and antiflatulents.

# **PART 332—ANTIPLATULENT PRODUCTS FOR OVER-THE-COUNTER HUMAN USE**

## **Subpart A—General Provisions**

Sec.

### **332.1 Scope.**

#### **Subpart B—Active Ingredients**

### **332.10 Antiflatulent active ingredients.**

### **332.15 Combination with non-antiflatulent active ingredients.**

#### **Subpart C—[Reserved]**

#### **Subpart D—Labeling**

### **332.30 Labeling of antiflatulent products.**

### **332.31 Professional labeling.**

#### **Subpart A—General Provisions**

### **§ 332.1 Scope.**

An over-the-counter antiflatulent product in a form suitable for oral ad-

ministration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

#### **Subpart B—Active Ingredients**

### **§ 332.10 Antiflatulent active ingredients.**

Simethicone; maximum daily dose 500 mg. There is no dosage limitation at this time for professional labeling.

### **§ 332.15 Combination with non-antiflatulent active ingredients.**

An antiflatulent may contain any generally recognized as safe and effective antacid ingredient(s) if it is indicated for use solely for the concurrent symptoms of gas associated with heartburn, sour stomach or acid indigestion.

#### **Subpart C—[Reserved]**

#### **Subpart D—Labeling**

### **§ 332.30 Labeling of antiflatulent products.**

(a) *Indications.* The labeling of the product represents or suggests the product as an "antiflatulent" and/or "to alleviate or relieve the symptoms of gas."

(b) *Directions for use.* The labeling of the product contains the recommended dosage per time interval (e.g., every 4 hours) or time period (e.g., 4 times a day) broken down by age groups if appropriate, followed by "except under the

advice and supervision of a physician." The words "or as needed" may be used after the recommended dosage per time interval or time period.

### **§ 332.31 Professional labeling.**

(a) The labeling of the product provided to health professionals (but not to the general public) may contain as additional indications postoperative gas pain or for use in endoscopic examination.

(b) Professional labeling for an antiflatulent-antacid combination may contain information allowed for health professionals for antacids and antiflatulents.

*Effective date.* This order shall become effective on July 5, 1974, except that all labeling for products not receiving an extension of the effective date for reformulation shall become effective on June 4, 1975, and where reformulation is necessary and an extension is granted shall become effective on June 4, 1976. The labeling of a product to health professionals shall after June 4, 1976, contain the neutralizing capacity of the product as calculated using the procedure set forth in § 331.26.

Dated: May 29, 1974.

A. M. SCHMIDT,  
Commissioner of Food and Drugs.  
[FR Doc. 74-12668 Filed 6-3-74; 8:45 am]

## Health Publications

o Comments

# What's in an antacid?

FDA Consumer, Jan-Feb, 1992 by Tom Cramer

The opposite of an acid is a base, and that's exactly what antacids are.

But a base all by itself can't neutralize the acid inside you. For reasons that are best explained on a blackboard in chemistry class, a base needs some chemical helpers," or ingredients, to accompany it on its neutralizing mission into your stomach.

All antacids contain at least one of the four primary "helpers" or ingredients: sodium, calcium, magnesium, and aluminum.

Here's a brief rundown of the composition and some potential side effects of various antacids:

**Sodium (Alka-seltzer, Bromo Seltzer, and others)**

Sodium bicarbonate or baking soda, perhaps the best known of the sodium-containing antacids, is potent and fast-acting. As its name suggests, it's heavy in sodium. If you're on a salt-restricted diet, and especially if the diet is intended to treat high blood pressure, take a sodium-containing antacid only under a doctor's orders.

**Calcium (Tums, Alka-2, Titralac, and others)**

Antacids in the form of calcium carbonate or calcium phosphate are potent and fast-acting.

Regular or heavy doses of calcium (more than five or six times per week) can cause constipation. Heavy and extended use of this product may clog your kidneys and cut down the amount of blood they can process, and can also cause kidney stones.

**Magnesium (Maalox, Mylanta, Camalox, Riopan, Gelusil, and others)**

Magnesium salts come in many forms--carbonate, glycinate, hydroxide, oxide, trisilicate, and aluminosilicates. Magnesium has a mild laxative effect; it can cause diarrhea. For this reason, magnesium salts are rarely used as the only active ingredients in an antacid, but are combined with aluminum, which counteracts the laxative effect. (The brand names listed above all contain magnesium-aluminum combinations.)

Like calcium, magnesium may cause kidney stones if taken for a very prolonged period, especially if the kidneys are functioning improperly to begin with. A serious magnesium overload in the bloodstream (hypertmagnesemia) can also cause blood pressure to drop, leading to respiratory or cardiac depression-a potentially dangerous decrease in lung or heart function.

Aluminum (Rolaids, AlternaGEL, Amphogel, and others)

Salts of aluminum (hydroxide, carbonate gel, or phosphate gel) can also cause constipation. For these reasons, aluminum is usually used in combination with the other three primary ingredients.

Used heavily over an extended period, antacids containing aluminum can weaken bones—especially in people who have kidney problems. Aluminum can cause dietary phosphates, calcium and fluoride to leave the body, eventually causing bone problems such as osteomalacia or osteoporosis.

It should be emphasized that aluminum-containing antacids present virtually no danger to people with normal kidney function who use these products only occasionally and as directed.

#### Simethicone

Some antacids contain an ingredient called simethicone, a gastric defoaming agent that breaks up gas bubbles, making them easier to eliminate from your body.

FDA says simethicone is safe and effective in combination with antacids for relief of gas associated with heartburn. But not all antacids contain this ingredient.

If you're looking for relief of symptoms associated with gas, read the antacid's label carefully to make sure it contains simethicone.

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## Review article: the management of heartburn in pregnancy

J. E. RICHTER

Department of Medicine, Temple University School of Medicine, Philadelphia, PA, USA

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### SUMMARY

Heartburn is a normal consequence of pregnancy. The predominant aetiology is a decrease in lower oesophageal sphincter pressure caused by female sex hormones, especially progesterone. Serious reflux complications during pregnancy are rare; hence upper endoscopy and other diagnostic tests are infrequently needed. Gastro-oesophageal reflux disease during pregnancy should be managed with a step-up algorithm beginning with

lifestyle modifications and dietary changes. Antacids or sucralfate are considered the first-line drug therapy. If symptoms persist, any of the histamine<sub>2</sub>-receptor antagonists can be used. Proton pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease. All but omeprazole are FDA category B drugs during pregnancy. Most drugs are excreted in breast milk. Of systemic agents, only the histamine<sub>2</sub>-receptor antagonists, with the exception of nizatidine, are safe to use during lactation.

### INTRODUCTION

Heartburn is estimated to occur in 30–50% of pregnancies, with the incidence approaching 80% in some populations.<sup>1</sup> Usually, heartburn during pregnancy resolves soon after delivery, however, sometimes it represents exacerbation of pre-existing gastro-oesophageal reflux disease. Most patients begin to note their symptoms late in the first trimester or second trimester of pregnancy with heartburn becoming more frequent and severe in the latter months of gestation. Although symptoms can be severe, oesophagitis is infrequent<sup>2</sup> and usually in patients with pre-existing disease. Reported risk factors for heartburn in pregnancy include gestational age, heartburn antecedent to the pregnancy and multiparity. Body mass index before pregnancy, weight gain during pregnancy, or race do not predict heartburn and older maternal age seems to have a protective effect.<sup>3</sup> Thus, heartburn is so common during pregnancy that patients and obstetricians both view it as a normal occurrence during a healthy pregnancy.

Nevertheless, the challenge of heartburn during pregnancy is patient and doctor concerns about the potential teratogenicity of common antireflux medications and the approximate step-up therapy for troubling symptoms. This review will address the treatment of gastro-oesophageal reflux disease during pregnancy and breast feeding as well as briefly summarizing the pathogenesis of this syndrome, clinical presentation and diagnostic work-up. The literature search for this review used online databases PubMed and MEDLINE, and relevant manuscripts published in English between 1966 and 2005 were reviewed. The search terms used included gastro-oesophageal reflux disease, heartburn in pregnancy, heartburn in lactation, antacids, Gaviscon, sucralfate, histamine<sub>2</sub>-receptor antagonists, proton-pump inhibitors and all the specific prescription drugs in the latter two drug classes. All abstracts were screened, potentially relevant articles were researched and bibliographies were reviewed.

### PATHOGENESIS

In the first trimester of pregnancy, basal lower oesophageal sphincter (LES) pressure may not change, but is less responsive to physiological stimuli (i.e. pentagastrin,

Correspondence to: Dr J. E. Richter, Department of Medicine, Temple University School of Medicine, 3401 North Broad Street, 800 Parkinson Pavilion, Philadelphia, PA 19140, USA.  
E-mail: jrichter@temple.edu

edrophonium chloride, methacholine or a protein meal) that usually increase LES pressure.<sup>1, 4</sup> In the later two trimesters, LES pressure gradually falls approximately 33–50% of basal values reaching a nadir at 36 weeks of gestation and rebounds to prepregnancy values 1–4 weeks postpartum.<sup>5</sup> Animal and human studies find that the increased circulating levels of progesterone during pregnancy mediate the LES relaxation, but oestrogen is a necessary primer.<sup>1</sup> The secondary role of increased abdominal pressure because of the enlarging gravid uterus is more controversial. All studies agree intra-abdominal pressure increases with pregnancy. It is unknown whether the normal compensatory response of the LES to increase to these changes is impaired during pregnancy.<sup>1</sup> Others have suggested that abnormal gastric emptying or delayed small bowel transit might contribute to heartburn in pregnancy.

#### CLINICAL PRESENTATION DURING PREGNANCY

The symptoms of heartburn during pregnancy do not differ from the classical presentation in the general adult population. Heartburn is the predominate symptom and worsens as pregnancy advances. Regurgitation occurs in about the same frequency as heartburn. The majority of patients report exacerbation of symptoms with eating and at bedtime.<sup>2</sup> Some patients will eat only one meal a day because of intense postprandial symptoms and others will need to sleep upright in a chair. Complications of gastro-oesophageal reflux disease (GERD) during pregnancy, especially oesophagitis and stricture formation, are rare. This observation should not be surprising since the reflux of pregnancy is generally of short duration without a background of chronic GERD.

#### DIAGNOSIS IN THE PREGNANT PATIENT

As in the non-pregnant patient, the initial diagnosis of GERD in pregnancy can reliably be made based on symptoms alone.<sup>6</sup> Barium radiographs are not necessary and should be avoided because of radiation exposure to the fetus. Oesophageal manometry and pH studies are rarely necessary during pregnancy but can be performed safely. Upper gastrointestinal (GI) endoscopy is the procedure of choice to evaluate intractable reflux symptoms or complications. This procedure can be safely performed without harm to the mother or fetus by carefully monitoring blood pressure and oxygen and judicious use of conscious sedation and fetal monitor-

Table 1. FDA classification of drugs for pregnancy

| FDA classification | Definition   |
|--------------------|--|
| Category A         | Well controlled studies in humans show no fetal risk   |
| Category B         | Animal studies show no risks, but human studies inadequate or animal studies show some risk not supported by human studies |
| Category C         | Animal studies show risk but human studies are inadequate or lacking or no studies in humans or animals                    |
| Category D         | Definite fetal abnormalities in human studies but potential benefits may outweigh the risks                                |
| Category X         | Contraindicated in pregnancy, fetal abnormalities in animals or humans. Risks outweigh benefits                            |

ing.<sup>2, 7, 8</sup> Midazolam and diazepam are category D, fentanyl is category C and meperidine and propofol are category B drugs during pregnancy (Table 1). Although not approved by the FDA for these indications during pregnancy, clinical experience suggests that these medications are safe with appropriate monitoring, particularly after the first trimester.<sup>7, 8</sup>

#### MEDICAL TREATMENT OF GERD DURING PREGNANCY

The challenge of treatment during pregnancy is the potential teratogenicity of common antireflux medications. Lifestyle modification is the key for treating mild symptoms. Smaller meals, not eating late at night, elevation of the head of the bed and avoiding foods and medications causing heartburn usually relieve the mild symptoms seen in early pregnancy. Chewing gum stimulates the salivary glands and can help neutralize acid. Abstinence from alcohol and tobacco are encouraged to reduce reflux symptoms and to avoid fetal exposure to these harmful substances.

For more troubling reflux symptoms, the doctor must discuss with the patient the benefits vs. the risk of drug therapy. Informed consent is appropriate. Nearly all medications are not tested in randomized-controlled studies in pregnant women because of ethical and medicolegal concerns. Most recommendations on drug safety arise from case reports and cohort studies by doctors, pharmaceutical companies or the FDA. Voluntary reporting by the manufacturer's suffers from



unknown duration of follow-up, absence of appropriate controls and possible reporting bias.<sup>9</sup>

Commonly used medications include antacids, sucralate, histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs), pro-motility drugs and proton-pump inhibitors (PPIs). The incidence of major fetal malformations in the general population ranges between 1% and 3%.<sup>10</sup> The FDA divides the safety of drugs during pregnancy into five categories (A, B, C, D and X) based on systemic absorption and reports of congenital defects in animals or humans (Table 1).<sup>11</sup>

The teratogenic period ranges from day 31 (in a 28-day menstrual cycle) to day 71 from the last menstrual period,<sup>10</sup> essentially the first 10 weeks of gestation. This represents the critical period of organogenesis. Before day 31, exposure to a teratogen usually

causes an all-or-none effect; either the fetus dies or survives without anomalies. Fetal cells are totipotent during this time period with respect to organogenesis; therefore, if a few cells die, the remaining cells can replace their function. Drugs that are not urgently required should be withheld until after the teratogenic period, although drugs can still affect the fetus in later gestation. Drugs used for GERD during pregnancy and their FDA categories are summarized in Table 2.

#### Antacids

Antacids are fast and effective at relieving the symptoms of heartburn and are preferred by patients as a result of the immediate symptom relief provided. About 30–50% of women will only require antacids to ease their

Table 2. FDA classification of drugs used for gastro-oesophageal reflux disease in pregnancy

| Drugs  | FDA class | Comments  |
|--|-----------|---|
| <b>Antacids</b>  |           |   |
| Aluminium-, calcium- or magnesium-containing antacids              | None      | Most are safe for use during pregnancy and for aspiration prophylaxis during labour because of minimal absorption   |
| Magnesium trisilicates   | None      | Avoid long-term, high-dose therapy in pregnancy   |
| Sodium bicarbonate   | None      | Not safe for use in pregnancy as causes fluid overload and metabolic alkalosis  |
| <b>Mucosal protectant</b>  |           |   |
| Sucralfate   | B         | No teratogenicity in animals. Generally regarded as acceptable for human use because of minimal absorption  |
| <b>Histamine<sub>2</sub>-receptor antagonist (H<sub>2</sub>RA)</b> |           |   |
| Cimetidine   | B         | A prospective, controlled study suggests acceptable for use in humans   |
| Ranitidine   | B         | Same as above. Ranitidine is the only H <sub>2</sub> RA whose efficacy during pregnancy has been established  |
| Famotidine   | B         | Same as cimetidine, but paucity of safety data in humans  |
| Nizatidine   | B         | Not recommended during pregnancy. In animals, spontaneous abortion, congenital malformations, low birth weight and fewer live births have been reported. Little data in humans        |
| <b>Promotility agents</b>  |           |   |
| Cisapride  | C         | Embryotoxic and fetotoxic in animals. Recent prospective controlled study in humans suggests acceptable in pregnancy, but drugs recently removed by FDA for fatal cardiac arrhythmias |
| Metoclopramide   | B         | No teratogenic effects in animals or humans reported  |
| <b>Proton-pump inhibitors</b>                                      |           |   |
| Omeprazole   | C         | Embryotoxic and fetotoxic in animals. Case reports in human suggest similar concerns. Acceptable for use for aspiration prophylaxis in labour   |
| Lansoprazole   | B         | No fetal teratogenicity or harm. Limited human pregnancy data   |
| Rabeprazole  | B         | Use is acceptable for aspiration prophylaxis during pregnancy   |
| Pantoprazole   | B         | No fetal teratogenicity or harm. Limited human pregnancy data   |
| Esomeprazole   | B         | Use is acceptable for aspiration prophylaxis during pregnancy   |
|  |           | No fetal teratogenicity or harm. Limited human pregnancy data   |
|  |           | Use is acceptable for aspiration prophylaxis during pregnancy   |



heartburn of pregnancy. Only limited data exist concerning the effects of antacids on the fetus with no controlled trials of efficacy. Magnesium-, aluminium-, or calcium-containing antacids are not teratogenic in animal studies,<sup>12</sup> although 15–30% of magnesium and a smaller percentage of aluminium preparations are absorbed after reacting with hydrochloric acid.

One retrospective, case-controlled study in the 1960s<sup>13</sup> reported a significant increase in major and minor congenital malformations in infants exposed to antacids during the third trimester of pregnancy. However, analysis of individual antacids (aluminium hydroxide, sodium bicarbonate, magnesium trisilicate and calcium carbonate) found no association with increased congenital anomalies. A recent European consensus conference recommended calcium/magnesium-based antacids for pregnant women because of their safety profile.<sup>14</sup> These experts found that calcium-based antacids had the added benefit of increasing calcium supplementation to prevent the hypertension and pre-eclampsia associated with pregnancy. In addition, a large, randomized placebo-controlled trial found that magnesium sulphate supplementation reduces the risk of eclampsia by 50% compared with placebo, and may also reduce the risk of maternal death, with no serious short-term side-effects.<sup>15</sup>

Alginates form a strong, non-systemic barrier in the stomach, preventing reflux of acid and food into the oesophagus. They are usually combined with antacids and marketed under the general label of Gaviscon. Recently, a form of Gaviscon with less sodium per dose was studied in an open-label multicentre study in 150 pregnant women over 4 weeks. Overall, the investigator's and women's rating of efficacy was 'very good' or 'good' in 88% and 90% of women, respectively, with most women (57%) reporting symptom relief within 10 min.<sup>16</sup> However, 10 adverse events were reported in 10 fetuses (three episodes of fetal distress) and others report that Gaviscon compounds containing magnesium trisilicate can cause fetal nephrolithiasis, hypotonia, respiratory distress and cardiovascular impairment if used long-term and at high doses.<sup>11</sup>

Antacids containing sodium bicarbonate should be avoided during pregnancy because they cause maternal or fetal metabolic alkalosis and fluid overload. Antacids should be taken at a different time than supplemental iron, because normal gastric acid facilitates the absorption of iron.

### *Sucralfate*

Sucralfate, an aluminium salt of a sulphated disaccharide, inhibits pepsin activity and protects against ulcers. It is poorly absorbed from the GI tract, exerting its mucosal protection through a local, rather than systemic action. Each gram of sucralfate contains 207 mg of aluminium.<sup>16</sup> The potential fetal toxicity of sucralfate relates to its aluminium content.

Sucralfate is the only non-absorbable drug that has been studied in a randomized-controlled study during pregnancy. In an Italian study,<sup>17</sup> 42 women were given sucralfate 1 g three times daily and compared with 24 women given information on dietary and lifestyle modifications. Sucralfate-treated patients had a higher frequency of remission of heartburn and regurgitation symptoms at 1 month than controls (90% vs. 43% and 83% vs. 27%, respectively). No maternal or fetal adverse events were reported.

In several animal models, sucralfate did not affect fertility and was not teratogenic with doses up to 50 times those used in humans.<sup>16</sup> Likewise, human fetal toxicity has not been reported. For example, in a surveillance study of 229 101 pregnancies in Michigan Medicaid patients evaluated between 1985 and 1992, 185 newborn babies were exposed to sucralfate in the first trimester. Five birth defects were observed, whereas eight were expected.<sup>16</sup> Therefore, sucralfate is an FDA category B drug.

### *Promotility drugs*

**Metoclopramide.** Metoclopramide, an antidopaminergic drug, improves GER by increasing LES pressure, improving oesophageal acid clearance and promoting gastric emptying. Its major use in pregnancy is for the treatment of nausea and vomiting. Reproductive studies in animals in doses up to 250 times the recommended human dose reveal no evidence of impaired fertility or fetal toxicity.<sup>18</sup> Congenital malformations or fetal toxicity because of metoclopramide have not been reported in humans. In the Michigan Medicaid Surveillance Study,<sup>16</sup> 10 (5.2%) major birth defects were reported in 992 newborns exposed to metoclopramide during the first trimester (eight were expected). Metoclopramide is designated a category B drug during pregnancy.

**Cisapride.** Cisapride promotes the release of acetylcholine from the myenteric plexus, thereby increasing LES pressure, improving acid clearance and promoting

gastric emptying. The drug is toxic to the fetuses of rats and rabbits at doses 112 times the recommended human dose, resulting in lower birth weights and decreased survival.<sup>19</sup>

Human reports suggest cisapride is safe during pregnancy. In a prospective, multicentre study, the outcome of 129 Canadian women who took cisapride during pregnancy between November 1996 and November 1998 were compared with a control group.<sup>20</sup> The mean daily cisapride dose was 25 mg (range: 5–120) and the mean length of exposure was 4.6 weeks (range: 0.14–41). Most women took cisapride during the first trimester (88%), 3% of women took it throughout their pregnancy. Most women were also taking multiple other antireflux medications, including antacids, H<sub>2</sub>RAs and PPIs. Investigators found no differences in rates of major or minor congenital malformations in the cisapride group compared with the matched controls. In 1998, an observational cohort study described the outcome of 12 pregnancies in women taking cisapride during the first trimester in England.<sup>21</sup> The outcomes included two elective abortions, one lost to follow-up and 10 normal term babies. In two other cases, cisapride was taken during the second or third trimesters and healthy babies were born.

Cisapride is designated a category C drug in pregnancy because of its toxicity in animals. In July 2000, Janssen Pharmaceutical removed cisapride from the market and it now is only available in a limited-access program. High cisapride blood levels, because of other drugs interfering with its metabolism by the cytochrome P-450 3A4 enzyme, caused serious cardiac arrhythmias in more than 400 cases, including 80 fatalities.<sup>22</sup>

#### *Histamine<sub>2</sub>-receptor antagonists*

The H<sub>2</sub>RAs are the most commonly used and safest medications for the pregnant woman with heartburn not responding to lifestyle modification and non-absorbable medication. All four drugs (cimetidine, ranitidine, famotidine and nizatidine) are FDA approved category B drugs for pregnancy.

*Cimetidine and ranitidine.* Cimetidine and ranitidine have had considerable use in pregnancy over the last 30 years with an excellent safety profile. Only ranitidine's efficacy has been specifically studied during pregnancy. In a double-blind, placebo-controlled, triple-crossover study, Larson *et al.*<sup>23</sup> compared ranitidine once or twice daily

with placebo in pregnant heartburn subjects not responding to antacids and lifestyle modification. Twenty women at least 20 weeks gestation were studied assessing symptom response and antacid use by daily diaries. In the 18 women completing the 4-week study, only ranitidine 150 mg b.d. reduced symptoms and antacid usage compared with baseline values ( $P < 0.001$ ) or with placebo ( $P < 0.001$ ). The average heartburn reduction was 55.6% (95% CI: 34.8–76.5) compared with baseline and 44.2% (95% CI: 15.4–72.9) when compared with placebo. No adverse pregnancy outcomes or drug reactions were noted.

In animal studies, cimetidine has a weak antiandrogenic effect in animals, as evidenced by a reduction of the size of testes, prostate glands and seminal vesicles.<sup>24</sup> Ranitidine has no antiandrogenic activity in animals.<sup>25</sup> Neither H<sub>2</sub>RA has reports of human sexual defects in infants.

To date, the safety of cimetidine and ranitidine has been assessed in over 2000 pregnancies in database studies not sponsored by the manufacturers. In the surveillance study of 229 101 pregnancies in the Michigan Medicaid recipients between 1985 and 1992,<sup>16</sup> 460 newborns were exposed to cimetidine and 560 newborns were exposed to ranitidine during the first trimester. Twenty (4.3%) major birth defects were observed with cimetidine and 23 (4.5%) with ranitidine, a rate similar (4.3%) to that reported in women taking no medications during their pregnancies. In a 1996 prospective cohort study, 178 women exposed during pregnancy to H<sub>2</sub>RAs were matched with 178 women with no exposure with similar maternal age, smoking and alcohol history.<sup>26</sup> Among these subjects, 71% took ranitidine, 16% cimetidine, 8% famotidine and 5% nizatidine. The outcomes of both groups were similar in terms of live births, spontaneous or elective abortions, gestational age at delivery, birth weight or major malformation. The latter rate was 2.1% in subjects exposed to H<sub>2</sub>RAs vs. 3.0% in the non-exposed cohorts.

The Swedish Medical Birth Registry in 1998 reported on 553 babies delivered by 547 women using various acid-suppressing medications in early pregnancy.<sup>27</sup> Seventeen infants had congenital defects (3.1%, 95% CI: 1.8–4.9) compared with the expected rate of 3.9% in the Registry among women not taking any medications. Of the 17 infants, 10 had been exposed to PPIs, six to H<sub>2</sub>RAs and one to both class of drugs. Two birth defects (5.7%) in 35 infants exposed to cimetidine and six defects (3.8%) in 156 infants exposed to ranitidine were reported. Overall, the odds ratio for malformations after

H<sub>2</sub>RAs was 0.46 (95% CI: 0.17–1.20) in contrast to 0.91 (95% CI: 0.45–1.84) for infants exposed to PPIs, early during pregnancy. Finally, two databases, one from England and another from Italy, were combined in a study published in 1999, which compared the incidence of congenital malformations in infants and women receiving cimetidine, ranitidine or omeprazole during the first trimester of pregnancy with unexposed control women.<sup>28</sup> The relative risk of malformation (adjusted for maternal age and prematurity) were similar among all three drugs: cimetidine (1.3%, 95% CI: 0.7–2.6), ranitidine 1.5 (95% CI: 0.9–2.6) and omeprazole 0.9 (95% CI: 0.4–2.4).

In summary, cimetidine and ranitidine have not been associated with an increased risk of congenital malformations. Ranitidine is the only H<sub>2</sub>RA with documented efficacy in pregnancy. Some authorities have recommended that cimetidine not be used during pregnancy because of possible feminization as observed in some animals and non-pregnant humans.<sup>29</sup>

**Famotidine and nizatidine.** There are much less reported safety data with these latter H<sub>2</sub>RAs than cimetidine and ranitidine. Animal studies with famotidine revealed no fetal toxicity or teratogenicity.<sup>30</sup> However, pregnant rabbits with the equivalent of 300 times the recommended human dose of nizatidine encountered abortions, low fetal weights and fewer live fetuses.<sup>31</sup> On the contrary, rat studies found no adverse effects on the fetal pups.<sup>32</sup>

In the Michigan Medicaid Surveillance Study,<sup>16</sup> two (6.1%) of 33 fetuses exposed to famotidine during the first trimester of pregnancy developed major birth defects compared with the expected prevalence of one. The small size was too small to draw firm conclusions, however. With nizatidine there is only a single case report of a woman delivering a healthy baby after taking the drug during 14–16 weeks of gestation.<sup>16</sup>

Although few reports are available, famotidine appears safe during pregnancy. Although nizatidine was previously classified as category C, the FDA recently reclassified it as a category B drug. However, the conflicting animal data are troublesome and suggest that other H<sub>2</sub>RAs may be safer during pregnancy.

#### Proton-pump inhibitors

Proton-pump inhibitors are the most effective drug therapy for symptom control and healing of oesopha-

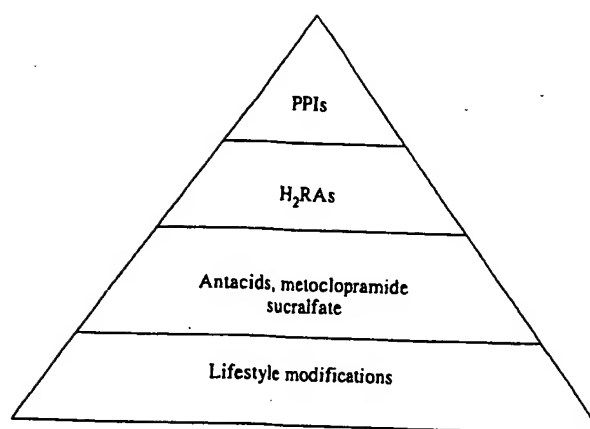


Figure 1. The pyramid of medical therapy for gastro-oesophageal reflux disease (GERD) in the pregnant woman with heartburn. Unlike the non-pregnant patient, step-up therapy is preferred and proton-pump inhibitors (PPIs) reserved for the women with well-defined complicated GERD not responding to lifestyle changes, antacids or histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RAs).

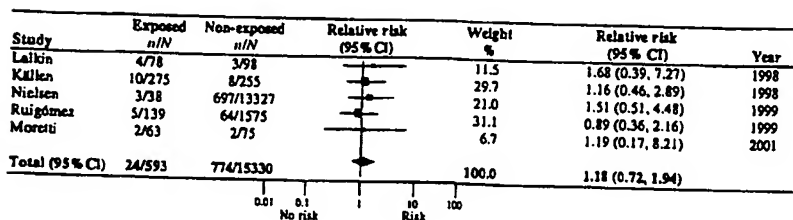
gitis. The PPIs have not been as extensively used in pregnancy as the H<sub>2</sub>RAs, or is their efficacy proven in pregnancy, and the data about total safety are more limited. Omeprazole is categorized as a class C drug by the FDA because of fetal toxicity. The other PPIs are categorized as class B drugs. However, unlike the non-pregnant heartburn patient, PPIs should only be used during pregnancy in women with well-defined complicated GERD, not responding to lifestyle changes, antacids and H<sub>2</sub>RAs (Figure 1).

**Omeprazole.** Omeprazole, the first of the PPIs, is classified as a class C drug in pregnancy because at doses similar to those used in humans, omeprazole produced dose-related embryonic and fetal mortality in pregnant rats and rabbits.<sup>33</sup> No teratogenicity was observed.

The FDA has received reports of at least 12 birth defects in pregnant women exposed to omeprazole, including anencephaly and hydrocephaly.<sup>16</sup> However, other case reports<sup>34</sup> and small case series<sup>21, 35</sup> have found no infant congenital malformations in mothers taking 20–60 mg omeprazole/day, even in the first trimester of pregnancy.

A recent meta-analysis assessed the risks of congenital fetal malformations in women using PPIs in the first trimester of pregnancy.<sup>36</sup> Five studies met the inclusion criteria, all were cohort studies ascertaining pregnancy outcomes with either registry linkage<sup>27, 28, 37</sup> or by direct interview with the mother.<sup>36, 38</sup> A total of 593 infants were exposed to PPIs, most (534) received

Figure 2. Individual and summary relative risk for studies including all proton-pump inhibitor exposures (from Ref.<sup>36</sup> with permission).



omeprazole. The summary relative risk for all major malformations among any PPI exposure was 1.18 (95% CI: 0.72–1.94), a non-significant relative risk ( $P = 0.7$ ). For the four studies where data for only omeprazole could be extracted (Figure 2), the summary relative risk was 1.05 (95% CI: 0.59–1.85), also indicating a non-significant relative risk for malformations.

Although the weight of evidence suggests omeprazole is safe in pregnancy, the FDA has not changed its class C rating. With the advent of newer PPIs, especially esomeprazole, omeprazole is currently infrequently prescribed. However, the drug is now over-the-counter at a 20 mg dose and cheaper than prescription PPIs.

**Lansoprazole.** Animal studies using doses of lansoprazole up to 40 times the recommended human dose have found no evidence of impaired fertility or fetal toxicity.<sup>39</sup>

Human data on the safety of lansoprazole in pregnancy are more limited. In one non-observational cohort study,<sup>21</sup> six pregnant patients taking lansoprazole during the first trimester delivered seven healthy newborns. Lansoprazole was the only acid-suppressing drug exposure in 13 infants reported to the Swedish Medical Birth Registry.<sup>27</sup> Two birth defects were observed; one atrial septal defect and one undescended testes. In a Danish study published in 1999,<sup>37</sup> 38 patients had taken PPIs during the first trimester of pregnancy (35 omeprazole, three lansoprazole). The prevalence of major birth defects, low birth weight and prematurity were no different than in pregnant controls not receiving any medications. In a study published this year,<sup>40</sup> 295 pregnancies exposed to omeprazole, 62 to lansoprazole and 53 to pantoprazole were compared with 868 pregnant controls for the development of congenital abnormalities. As with other studies, the rate of congenital abnormalities did not differ between the exposed and control groups: omeprazole nine of 249 (3.6%), lansoprazole two of 51 (3.9%) and pantoprazole one of 48 (2.1%) vs. controls 30 of 792 (3.8%). No differences were found when exposure was limited to the first trimester.

The lack of teratogenicity in animals is reassuring, accounting for the FDA class C risk category for

lansoprazole use during pregnancy. However, the data on safety in human pregnancies are limited and avoidance of this PPI and all PPIs, especially during the first trimester, is the safest course. If lansoprazole is required, or if inadvertent exposure occurs early in gestation, the fetal risk seems to be low.

#### Newer PPIs

Based on product information from the individual manufacturers, the newer PPIs (rabeprazole, pantoprazole and esomeprazole) have been shown safe in various animal studies. No reports describing the use of these newer PPIs during human pregnancies are available.<sup>16</sup>

#### SAFETY OF MEDICAL TREATMENTS FOR GERD DURING LACTATION

The heartburn of pregnancy typically resolves shortly after delivery, although some women still experience symptoms postpartum requiring treatment. All systemic antireflux medications are excreted in breast milk and could harm the infant. Therapeutic options must be explained and discussed with women who require treatment but who want to breastfeed.

Drug safety during lactation has been assessed in animal studies and human case reports (Table 3). Aluminium and magnesium hydroxide antacids are not concentrated in breast milk and, thus, are safe during lactation. Neither Gaviscon nor sucralate have been studied during lactation, but are presumed safe because of limited maternal absorption.

All H<sub>2</sub>RAs are excreted in human breast milk. Cimetidine and ranitidine reach concentrations in breast milk four to seven times the doses present in maternal serum.<sup>41</sup> In contrast, famotidine only reaches a mean milk:plasma concentration of 1.78, 6 h after ingestions.<sup>42</sup> Small amounts of nizatidine are excreted into human breast milk.<sup>43</sup> In the only animal studies assessing H<sub>2</sub>RA safety during lactation, pups reared by lactating rats ingesting nizatidine experienced growth

Table 3. Safety of GERD medications during lactation

| Drugs                  | Safety | Comments   |
|------------------------|--------|--|
| Antacids               | Yes    | Not concentrated in breast milk  |
| Sucralfate             | Yes    | Minimal, if any, excretion in breast milk  |
| <b>H<sub>2</sub>RA</b> |        |  |
| Cimetidine             | Yes    | American Academy of Pediatrics classified as compatible with breast feeding  |
| Ranitidine             | Yes    | Excreted in breast milk in concentrations similar to cimetidine  |
| Famotidine             | Yes    | Lowest concentrations in breast milk of all H <sub>2</sub> RAs   |
| Nizatidine             | No     | Growth depression in pups of lactating rats  |
| Proton-pump inhibitors | No     | Little known of excretion in breast milk. Growth depression in pups of lactating rats receiving omeprazole and rabeprazole |

GERD, gastro-oesophageal reflux disease; H<sub>2</sub>RA, histamine<sub>2</sub>-receptor antagonist.

retardation.<sup>44</sup> The effects of H<sub>2</sub>RAs in breast milk on the nursing human infant are unknown. In 1994, the American Academy of Pediatrics classified cimetidine as compatible with breast feeding.<sup>45</sup> The present review also suggests that ranitidine and famotidine are safe and the latter H<sub>2</sub>RA may be preferred because of the lower concentration in human breast milk. Nizatidine should be avoided in the breast feeding mother because of the single animal study.<sup>44</sup>

Little is known about PPI excretion in breast milk or infant safety in lactating women. PPIs probably are excreted in human milk, because of their relatively low-molecular weight. This was confirmed in the only report of PPI use during breast feeding.<sup>46</sup> During the day, the patient fed her infant son just before taking omeprazole at 8:00 AM, refraining from nursing for 4 h, and then expressed and discarded her breast milk at noon. At 3 weeks postpartum, blood and milk samples were obtained at 8:00 AM, and then every 30 min for 4 h. Breast milk levels of omeprazole began to rise at 9:30 AM and peaked at 11:00 AM at 58 mM, considerably lower value than simultaneous maternal level of 950 mM. The infant was doing well at 1 year. However, rats administered omeprazole at 35–345 times and rabeprazole at a dose of 195 times the recommended human dose during late pregnancy and lactation had decreased body weight gain of their pups.<sup>33, 47</sup> Therefore, PPIs are not recommended for use by lactating

mothers. Women with severe GERD symptoms can either take PPIs and discontinue nursing or use a GERD medication (i.e. H<sub>2</sub>RA) from another class.

## CONCLUSION

Heartburn is a normal consequence of pregnancy, occurring in nearly two-thirds of women. The predominant cause is a decrease in LES pressure caused by female sex hormones, especially progesterone. Serious reflux complications (i.e. oesophagitis) during pregnancy are uncommon; therefore upper endoscopy and other diagnostic tests are usually not needed. Symptomatic GERD during pregnancy should be managed with a step-up algorithm beginning with lifestyle modifications and dietary changes (Figure 1). Antacids or sucralfate are considered the first-line medical therapy. If symptoms persist, any of the H<sub>2</sub>RAs can be used. Proton-pump inhibitors are reserved for women with intractable symptoms or complicated reflux disease. All but omeprazole are FDA category B drugs during pregnancy. Most drugs are excreted in breast milk. Of the systemic agents, only the H<sub>2</sub>RAs, with the exception of nizatidine, are safe to use during lactation.

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(12) **United States Patent**  
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SUPPLEMENTS AND METHOD OF MAKING**(75) Inventors: Gordon N. McGrew, Evanston, IL  
(US); David G. Barkalow, Deerfield,  
IL (US); Sonya S. Johnson, LaGrange  
Highlands, IL (US); David W. Record,  
River Forest, IL (US); Mansukh M.  
Patel, Downers Grove, IL (US); Jack  
D. Nimz, Wauconda, IL (US); Steven  
E. Zibell, Tinley Park, IL (US); Robert  
J. Yotka, Orland Park, IL (US);  
Michael J. Greenberg, Northbrook, IL  
(US); Rebecca A. Aumann, Chicago,  
IL (US); Daniel J. Zyck, North  
Riverside, IL (US); Daniel J. Sitler,  
Woodridge, IL (US); Jeffrey S. Hook,  
Lockport, IL (US); James R. Maxwell,  
Chicago, IL (US); Michael A. Reed,  
Merrillville, IN (US); Victor V. Gudas,  
Oak Lawn, IL (US); Phillip G. Schnell,  
Downers Grove, IL (US); Henry T.  
Tyrpln, Palos Park, IL (US); Michael  
P. Russell, Evergreen Park, IL (US);  
David L. Witkewitz, Bridgeview, IL  
(US); Joo H. Song, Chicago, IL (US);  
Donald J. Townsend, Moores Hill, IN  
(US); Donald A. Seifstad, Frankfurt,  
IL (US); Ronald L. Ream, Plano, IL  
(US); Christine L. Corriveau, Orland  
Park, IL (US); William J. Wokas,  
Bolingbrook, IL (US); Thomas M.  
Tongue, Joliet, IL (US)(73) Assignee: Wm. Wrigley Jr. Company, Chicago,  
IL (US)(\*) Notice: Subject to any disclaimer, the term of this  
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Primary Examiner—Arthur L Corbin

(74) Attorney, Agent, or Firm—Steven P. Shurtz; Brinks  
Hofer Gilson & Lione(57) **ABSTRACT**A method for producing a chewing gum with a controlled  
release active agent, as well as the chewing gum so  
produced, is obtained by physically modifying the release  
properties of the active agent, such as a nutraceutical or  
nutritional supplement, by coating and drying. The active  
agent is coated by encapsulation, partially coated by  
agglomeration, entrapped by absorption, or treated by mul-  
tiple steps of encapsulation, agglomeration, and absorption.  
The coated active agent is preferably then co-dried and  
particle sized to produce a release-modified active agent for  
use in chewing gum. The active agent may also be used in  
a coating on a chewing gum product, as part of a rolling  
compound applied to the chewing gum product, or as a part  
of the liquid in a liquid-center chewing gum product.

42 Claims, No Drawings



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# NUTRACEUTICALS OR NUTRITIONAL SUPPLEMENTS AND METHOD OF MAKING

## REFERENCE TO EARLIER FILED APPLICATIONS

The present application claims the benefit under 35 U.S.C. § 119(e) of the filing date of U.S. Provisional Patent Application No. 60/112,389, filed Dec. 15, 1998. The application is a continuation of PCT Application Ser. No. US99/29792, filed Dec. 14, 1999, which designated the United States. Said PCT application is a continuation-in-part of U.S. patent application Ser. No. 09/389,211, filed Sep. 2, 1999, now abandoned, a continuation-in-part of U.S. patent application Ser. No. 09/286,818, filed Apr. 6, 1999 and a continuation-in-part of U.S. patent application Ser. No. 09/308,972, filed May 27, 1999, now U.S. Pat. No. 6,165,516, which is a nationalization of PCT/US96/18977, filed Nov. 27, 1996. Each of the foregoing applications are hereby incorporated by reference.

## BACKGROUND OF THE INVENTION

The present invention relates to methods for producing chewing gum. More particularly, the invention relates to producing chewing gum containing an effective amount of an active medicament. Preferably, the active medicament that is added to the chewing gum has been treated to control its rate of release from chewing gum or the chewing gum formulation has been modified to control the release of medicament for maximum effectiveness.

In recent years, efforts have been devoted to controlling release characteristics of various ingredients in chewing gum. Most notably, attempts have been made to delay the release of sweeteners and flavors in various chewing gum formulations to thereby lengthen the satisfactory chewing time of the gum. Delaying the release of sweeteners and flavors can also avoid an undesirable overpowering burst of sweetness or flavor during the initial chewing period. On the other hand, some ingredients have been treated so as to increase their rate of release in chewing gum.

Besides sweeteners, other ingredients may require a controlled release from chewing gum. In certain embodiments, it is contemplated that the active medicament that is added to the gum is not generally released very readily. An active medicament may be encapsulated in a water soluble matrix such that, during the chewing period, the medicament may be released quickly, resulting in a fast release. This would allow chewing gum to be a carrier for an active medicament with these fast release characteristics.

In some instances, serious taste problems may arise because of the bitter nature of many active medicaments. A prolonged or delayed release of active medicaments would allow for the use of the active medicaments in gum, but the low level of release of such medicaments may keep the level of that agent below the taste threshold of the active medicaments and not give chewing gum a bitter taste quality. In addition, active medicaments may also have other unpleasant tastes that may be overcome by reducing the release rate of active medicaments from a chewing gum.

Another aspect of the present invention contemplates the use of encapsulation techniques. For example, it may be that active medicaments may also be unstable in a chewing gum environment. In such cases, various methods of encapsulation may be needed to improve stability of the active medicament. In other circumstances, active medicaments may not be readily released from the chewing gum matrix and their effect may be considerably reduced. In such a

situation, a fast release encapsulation may be needed to release active medicament from the gum matrix.

Other methods contemplated are methods of controlling release of active medicament from gum. These methods would be useful in not releasing the active medicament in the oral cavity during gum chewing, but allowing the active medicament to be ingested during chewing. This will keep the active medicament from becoming effective until after it enters the digestive track.

It is of course known to provide active medicaments to individuals for various purposes. These medicaments can be used to treat diseases and as such are typically referred to as drugs or medicaments. Likewise, the drugs or medicaments can be used for preventive purposes. Still, it is known to provide medicaments to an individual for a variety of non-medical purposes including enhancing performance or maintaining health.

There are a great variety of such medicaments. These medicaments run the gamut from stimulants such as caffeine to drugs such as analgesics, tranquilizers, cardiovascular products, as well as vitamins, minerals, and supplements. Some such medicaments are taken on an "as-needed" basis while other medicaments must be taken at regular intervals by the individual.

Typically, drugs or medicaments are administered parenterally or enterally. Of course, parenteral administration is the administration of the drug intravenously directly into the blood stream. Enteral refers to the administration of the drug into the gastrointestinal tract. In either case, the goal of the drug administration is to move the drug from the site of administration towards the systemic circulation.

Oral administration of drugs is by far the most common method of moving drugs towards systemic circulation. When administered orally, drug absorption usually occurs due to the transport of cells across the membranes of the epithelial cells within the gastrointestinal tract. Absorption after oral administration is confounded by numerous factors. These factors include differences down the alimentary canal in: the luminal pH; surface area per luminal volume; perfusion of tissue, bile, and mucus flow; and the epithelial membranes. See *Merck Manual* at page 2599.

A further issue affecting the absorption or orally administered drugs is the form of the drug. Most orally administered drugs are in the form of tablets or capsules. This is primarily for convenience, economy, stability, and patient acceptance. Accordingly, these capsules or tablets must be disintegrated or dissolved before absorption can occur. There are a variety of factors capable of varying or retarding disintegration of solid dosage forms. Further, there are a variety of factors that affect the dissolution rate and therefore determine the availability of the drug for absorption. See *Merck Manual* at page 2600.

When a drug rapidly dissolves from a drug product and readily passes across membranes, absorption from most site administration tends to be complete. This is not always the case for drugs given orally. Before reaching the vena cava, the drug must move down the alimentary canal and pass through the gut wall and liver, which are common sites of drug metabolism. Thus, the drug may be metabolized before it can be measured in the general circulation. This cause of a decrease in drug input is called the first pass effect. A large number of drugs show low bioavailability owing to an extensive first pass metabolism. The two other most frequent causes of low bioavailability are insufficient time in the GI tract and the presence of competing reactions. See *Merck Manual* at page 2602.

Bioavailability considerations are most often encountered for orally administered drugs. Differences in bioavailability can have profound clinical significance.

Although parenteral administration does provide a method for eliminating a number of the variables that are present with oral administration, parenteral administration is not a preferable route. Typically parenteral administration requires the use of medical personnel and is just not warranted nor practical for the administration of most agents and drugs, e.g., analgesics. Even when required, parenteral administration is not preferred due to patient concerns including comfort, infection, etc., as well as the equipment and costs involved.

There is therefore a need for an improved method of delivering drugs and agents to an individual.

### SUMMARY OF THE INVENTION

The present invention provides improved methods for delivering a medicament or active agent to an individual. To this end, chewing gum is provided including a medicament or active agent. The medicament or active agent is present within the chewing gum composition (the water soluble portion and/or insoluble base portion). It has been found that by chewing the gum, the medicament or active agent is released from the chewing gum into saliva. Possibly, saliva coats the oral tissues under the tongue (sublingual) and the sides of the mouth where the drug may partition from the saliva into the oral mucosa. Continuing to chew the chewing gum creates a pressure within the buccal cavity and may force the medicament or active agent or medicament directly into the systemic system of the individual through the oral mucosa contained in the buccal cavity. This greatly enhances the absorption of the drug into the systemic system as well as the bioavailability of the drug within the system.

Improved chewing gum formulations including medicaments and active agents are also provided by the present invention.

To this end, the present invention provides a method of drug delivery comprising the steps of: providing a chewing gum that includes a medicament in the chewing gum composition; chewing the chewing gum to cause the medicament to be released from the chewing gum composition into the buccal cavity of the chewer.

The active medicament may be any agent that is traditionally used as a medicament and lends itself to being administered through the oral cavity. Such active agents may be vitamins, cancer chemotherapeutics; antimycotics; oral contraceptives, nicotine or nicotine replacement agents, minerals, antibacterial agents, anesthetics, antitussives, diuretics, anti-inflammatories, antibiotics, AIDS medication, neurological drugs, antivirals, psychotherapeutic agents, anti-diabetic agents and cardiovascular agents, nutraceuticals and nutritional supplements.

Accordingly, an advantage of the present invention is to provide new methods for delivering medicaments or active agents to an individual.

Still further, an advantage of the present invention is to provide a method of delivering medicaments to an individual that provides for increase absorption and bioavailability as compared to medicaments that are designed to be absorbed in the GI tract.

Further, an advantage of the present invention is to provide a method of administering a medicament or agent to an individual at a lower level than is typically administered orally while still achieving the same effect.

Furthermore, an advantage of the present invention is to provide a method for administering drugs or agents to an individual that heretofore were administered parenterally.

Additionally, an advantage of the present invention is to provide a method of administering drugs that is more palatable than current methods.

Moreover, an advantage of the present invention is to provide an improved method for drug delivery.

The present invention also provides a method of producing chewing gum with physically modified active medicaments to control their release. Such active medicaments are added to a gum coating to deliver the active medicaments systemically without unpleasant tastes. The present invention also relates to the chewing gum so produced. Physically modified active medicaments may be added to sucrose-type gum formulations and sucrose-type coatings. The formulation may be a low or high moisture formulation containing low or high amounts of moisture containing syrup. Physically modified active medicaments may also be used in low or non-sugar gum formulations and coatings that use sorbitol, mannitol, other polyols or carbohydrates. Non-sugar formulations may include low or high moisture sugar-free chewing gums.

Active medicaments described herein may be combined or co-dried with bulk sweeteners typically used in chewing gum before the active medicaments are physically modified. Such bulk sweeteners are sucrose, dextrose, fructose and maltodextrins, as well as sugar alcohols such as sorbitol, mannitol, xylitol, maltitol, lactitol, hydrogenated isomaltulose and hydrogenated starch hydrolyzates.

The modified release rate noted above may be a fast release or a delayed release. The modified release of active medicaments may be obtained by encapsulation, partial encapsulation or partial coating, entrapment or absorption with high or low water soluble materials or water insoluble materials. The procedures for modifying the active medicaments include spray drying, spray chilling, fluid bed coating, coacervation, extrusion and other agglomerating and standard encapsulating techniques. The active medicaments also may be absorbed onto an inert or water-insoluble material. Active medicaments may be modified in a multiple step process comprising any of the processes, or a combination of the processes noted. Prior to encapsulation, active medicaments may also be combined with bulk sweeteners including sucrose, dextrose, fructose, maltodextrin or other bulk sweeteners, as well as sugar alcohols such as sorbitol, mannitol, xylitol, maltitol, lactitol, hydrogenated isomaltulose and hydrogenated starch hydrolyzates.

Prior to encapsulation, active medicaments may be combined with high-intensity sweeteners, including but not limited to thaumatin, aspartame, alitame, acesulfame K, saccharin acid and its salts, glycyrrhizin, cyclamate and its salts, stevioside and dihydrochalcones. Co-encapsulation of active medicaments along with a high-intensity sweetener may reduce the poor taste qualities of active medicaments and control the sweetener release with active medicaments. This can improve the quality of the gum product and increase consumer acceptability.

### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides improved methods for delivering medicaments and other active agents to an individual as well as improved formulations including such medicaments and agents. Pursuant to the present invention, a physically modified medicament or active is contained in

a chewing gum formulation. In contrast to some prior such formulations, the medicament or agent is contained directly in the chewing gum composition.

Accordingly, as the chewing gum is chewed, the physically modified active is released into the saliva. During continual chewing, the medicament or active in the saliva may be then forced due to the pressure created by the chewing gum through the oral mucosa in the buccal cavity. The oral mucosa favors drug absorption. In contrast to a typically oral ingested drug, wherein the solution is in contact too briefly for absorption to be appreciable through the oral mucosa, it is believed that during the chewing, the physically modified active agent and/or medicament remains in the buccal cavity and may be forced or partitioned through the oral mucosa. An increase in the absorption of the drug may be achieved as well as an increase in the bioavailability of the drug as compared to typical oral administration. The drug or active agent may be absorbed much quicker than if it was swallowed as in a typical oral administration. Indeed, the absorption approaches that of a parental administration and bioavailability may be also much greater than oral administration.

It is also possible that less physically modified medicament or active agent can be placed in the chewing gum than is typically orally administered to an individual to achieve an effect and the same bioequivalence can be achieved. In some instances, for certain drugs and agents, the administration of the medicament or agent using chewing gum through the buccal activity may provide an increase in therapeutic effect even as compared to parenteral administration.

For example, caffeine is commonly used as a stimulant to alleviate the effects of sleep deprivation. It is almost completely metabolized in the liver and therefore classified as a low clearance, flow independent drug. This means its rate of inactivation is unaffected by delivery to the liver and can only be modified by a change in the hepatic enzyme activity.

Data set forth in detail in U.S. patent application Ser. No. 09/386,818 herein incorporated by reference, suggests that the absorption rate constant ( $K_a$ ) is significantly increased when caffeine is administered through chewing gum versus a pill. This means that the caffeine is moving into the systemic circulation at a significantly faster rate. A similar change in the onset of dynamic response has also been noted, e.g., alertness and performance.

When caffeine is added to stick chewing gum at a level of about 0.2% to about 5%, caffeine imparts an intense bitterness to the chewing gum that lasts throughout the chewing period. The higher the level used, the stronger the bitterness. At about 0.2%, which is about 5 mg per 2.7 gram stick, the bitterness is below the threshold limit and is not readily discernible. Taste limits in stick chewing gum are generally about 0.4% (10 mg) to about 4% (100 mg) of caffeine in a stick of gum. The 60–80 mg level of caffeine is about the level of caffeine found in a conventional cup of coffee. The target level of caffeine in stick gum is about 40 mg per stick, with a range of about 25–60 mg, so that a five stick package of gum would contain about 200 mg of caffeine, or the equivalent of caffeine in two strong cups of coffee. However, at this level caffeine bitterness overwhelms the flavor initially and lasts throughout the chewing period.

For coated pellet gum, piece weight is generally about 1.5 grams per piece. However, one coated piece of gum is about equal to  $\frac{1}{2}$  piece of stick gum. Two pellets are equivalent to a stick of gum, and together weigh about 3 grams. The above-noted target level of 40 mg per stick is equivalent to

20 mg per coated piece, or a range of about 12 to 30 mg caffeine per piece. This is about 0.8% to about 2% caffeine in a piece of coated gum, or a target level of 1.3%.

Caffeine is a slightly water soluble substance and, therefore, has a moderately slow release from stick chewing gum. Caffeine is 2.1% soluble in water at room temperature, 15% soluble in water at 80° C. and 40% soluble in boiling water. This gives caffeine a moderately slow release as shown below:

| Chewing Time | % Caffeine Release |
|--------------|--------------------|
| 0 min        | —                  |
| 5 min        | 56                 |
| 10 min       | 73                 |
| 20 min       | 88                 |
| 40 min       | 97                 |

Generally, highly water soluble ingredients such as sugars in stick gum are about 80–90% released after only five minutes of chewing. For caffeine, only about 50% is released, while the other 50% remains in the gum after five minutes of chewing. After 20 minutes almost 90% of caffeine is released.

Even if caffeine is dissolved in hot water and mixed in the stick gum, when the gum is cooled or kept at room temperature, caffeine may return to its normal crystalline state and release at a rate similar to that shown above.

When a physically modified active such as caffeine is added to a gum stick, the active agent will have an increased water solubility, and release quickly into the mouth from the gum. Depending on the active agent, which may generally be non-water soluble, physically modifying the active agent by various forms at encapsulation will increase the release of the active agent from chewing gum. Most water soluble active agents can be modified by encapsulation to give a more uniform release from chewing gum. Depending on the active agent and the type of encapsulation used, the level released from the gum into the mouth can be adjusted for maximum effectiveness.

Other agents or medicaments may be included in the present invention. By the terms "active agent" the present invention refers to a compound that has a desired therapeutic or physiological effect once ingested and/or metabolized. The therapeutic effect may be one which decreases the growth of a xenobiotic or other gut flora or fauna, alters the activity of an enzyme, provides the physical relief from a malady (e.g., diminishes pain, acid reflux or other discomfort), has an effect on the brain chemistry of molecules that determine mood and behavior. Of course these are just examples of what is intended by therapeutic effect. Those of skill in the art will readily recognize that a particular agent has or is associated with a given therapeutic effect.

The active agent may be any agent that is traditionally used as a medicament and lends itself to being administered through the oral cavity. Such active agents may be vitamins, cancer chemotherapeutics; antimycotics; oral contraceptives, nicotine or nicotine replacement agents, minerals, analgesics, antacids, muscle relaxants, antihistamines, decongestants, anesthetics, antitussives, diuretics, anti-inflammatories, antibiotics, antivirals, psychotherapeutic agents, anti-diabetic agents and cardiovascular agents, bioengineered pharmaceuticals, nutraceuticals and nutritional supplements. Vitamins and co-enzymes that

may be delivered using this invention include but are not limited to water or fat soluble vitamins such as thiamin, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin, flavin, choline, inositol and paraminobenzoic acid, carnitine, vitamin C, vitamin D and its analogs, vitamin A

and the carotenoids, retinoic acid, vitamin E and vitamin K. Examples of cancer chemotherapeutics agents include but are not limited to cisplatin (CDDP), procarbazine, mechlorethamine, cyclophosphamide, camptothecin, ifosfamide, melphalan, chlorambucil, bisulfan, nitrosurea, dactinomycin, daunorubicin, doxorubicin, bleomycin, plicomycin, mitomycin, etoposide (VP16), tamoxifen, taxol, transplatin, 5-fluorouracil, vincristin, vinblastin and methotrexate or any analog or derivative variant thereof.

Antimicrobial agents that may be used include but are not limited to nafcillin, oxacillin, vancomycin, clindamycin, erythromycin, trimethoprim-sulphamethoxazole, rifampin, ciprofloxacin, broad spectrum penicillin, amoxicillin, gentamicin, ceftriaxone, cefotaxime, chloramphenicol, clavunate, sulbactam, probenecid, doxycycline, spectinomycin, cefixime, penicillin G, minocycline, P-lactamase inhibitors; mezicillin, piperacillin, aztreonam, norfloxacin, trimethoprim, ceftazidime, dapsone.

Antifungal agents that may be delivered include but are not limited to ketoconazole, fluconazole, nystatin, itraconazole, clotrimazole, and amphotericin B. Antiviral agents that may be used include but are not limited to acyclovir, trifluridine, idoxuridine, foscarnet, ganciclovir, zidovudine, dideoxycytosine, dideoxyinosine, stavudine, famciclovir, didanosine, zalcitabine, rimantadine, and cytokines.

Antacids include cimetidine, ranitidine, nizatidine, famotidine, omeprazole, bismuth antacids, metronidazole antacids, tetracycline antacids, clarithromycin antacids, hydroxides of aluminum, magnesium, sodium bicarbonates, calcium bicarbonate and other carbonates, silicates, and phosphates.

Antihistamines are represented by but are not limited to cimetidine, ranitidine, diphenhydramine, prylamine, promethazine, chlorpheniramine, chlorcyclizine, terfenadine, carbinoxamine maleate, clemastine fumarate, diphenhydramine hydrochloride, dimenhydrinate, prilamine maleate, tripeleminamine hydrochloride, tripeleminamine citrate, chlorpheniramine maleate, brompheniramine maleate, hydroxyzine pamoate, hydroxyzine hydrochloride, cyclizine lactate, cyclizine hydrochloride, meclizine hydrochloride, acrivastine, cetirizine hydrochloride, astemizole, levocabastine hydrochloride, and loratadine.

Decongestants and antitussives include agents such as dextromethorphan hydrobromide, levopropoxyphene napsylate, noscapine, carbetapentane, caramiphen, chlophedianol, pseudoephedrine hydrochloride pseudoephedrine sulfate, phenylephrine, diphenhydramine, guaifenesin, pholcodine, and benzonate.

Anesthetics include etomidate, ketamine, propofol, and benodiazepines (e.g., chlordiazepoxide, diazepam, clonazepam, halazepam, flurazepam, quazepam, estazolam, triazolam, alprazolam, midazolam, temazepam, oxazepam, lorazepam), benzocaine, dyclonine, bupivacaine, etidocaine, lidocaine, mepivacaine, promoxine, prilocaine, procaine, proparcaine, ropivacaine, tetracaine. Other useful agents may include amobarbital, aprobarbital, butabarbital, butalbital mephobarbital, methohexital, pentobarbital, phenobarbital, secobarbital, thiopental, paral, chloralhydrate, ethchlorvynol, clutethimide, methpyrrolon, ethinamate, and meprobarnate.

Analgesics include opioids and other medicaments such as morphine, mepidine, dentanyl, sufentanil, alfentanil, aspirin, acetaminophen, ibuprofen, indomethacin, naproxen, atrin, isocome, midrin, axotal, firinal, phrenilin, ergot, and ergot derivatives (wigraine, cafergot, ergostat, ergomar, dihydroergotamine), imitrex, and ketoprofen.

Diuretics include but are not limited to acetazolamide, dichlorphenamide, methazolamide, furosemide, bumetanide, ethacrynic acid torseimide, azosemide, muzolimine, pirtanide, tripamide, bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichlormethiazide, indapamide, metolazone, quinethazone, amiloride, triamterene, sprion olactone, canrenone, and potassium canrenoate.

Anti-inflammatories include but are not limited to salicylic acid derivatives (e.g. aspirin), indole and indene acetic acids (indomethacin, sulindac and etodolac) heteroaryl acetic acids (tolmetin diclofenac and ketorolac) aryl propionic acid derivatives (ibuprofen, naproxen, ketoprofen, fenopren, oxaprozone), anthranilic acids (mefenamic acid, meclofenamic acid) enolic acids (piroxicam, tenoxicam, phenylbutazone and oxyphenbutazone).

Psychotherapeutic agents include thiorazine, serentil, mellaril, millazin, miltal, permitil, prolixin, trilafon, stelazine, suprazine, taractan, naven, clozaril, baldol, halperon, loxitane, moban, orap, risperdal, alprazolam, chordiaepoxide, clonazepam, clonazepam, diazepam, halazepam, lorazepam, oxazepam, prazepam, buspirone, elvavil, anafranil, adapin, sinequan, tofranil, surmontil, asendin, norpramin, pertofrane, ludiomil, pamelor, vivactil, prozac, luvox, paxil, zoloft, effexor, wellbutrin, serzone, desyrel, nardil, parnate, eldepryl.

Cardiovascular agents include but are not limited to nitroglycerin, isosorbide dinitrate, sodium nitroprusside, captopril, enalapril, enalaprilat, quinapril, lisinopril, ramipril, losartan, amrinone, linnone, vesnerinone, hydralazine, nicorandil, prozasin, doxazosin, bunazosin, tamutolin, yohimbine, propranolol, metoprolol, nadolol, atenolol, timolol, esmolol, pindolol, acebutolol, labetalol, phentolamine, carvedilol, bucindolol, verapamil, nifedipine, amlodipine and dobutamine, or a sexual dysfunction agent like sildenafil citrate (Viagra).

It is envisioned that depending on the active agent or medicament, the resultant chewing gum can be used to treat inter alia: coughs, colds, motion sickness; allergies; fevers; pain; inflammation; sore throats; cold sores; migraines; sinus problems; diarrhea; diabetes; gastritis; depression; anxiety, hypertension; angina and other maladies and symptoms. Also these gums may be useful in ameliorating cravings in substance abuse withdrawal or for appetite suppression. Specific active agents or medicaments include by way of example and limitation: caffeine, aspirin, acetaminophen; ibuprofen; ketoprofen; cimetidine, ranitidine, famotidine, dramamine, omeprazole, dyclonine hydrochloride, chlorpheniramine maleate, pseudoephedrine hydrochloride, dextromethorphan hydrobromide; benzocaine, sodium naproxen, and nicotine.

Compositions that may be formulated into a suitable chewing gum formulation are described in, for examples, U.S. Pat. No. 5,858,423; U.S. Pat. No. 5,858,413; U.S. Pat. No. 5,858,412 and U.S. Pat. No. 5,858,383. Additionally, Goodman and Gilman's "The Pharmaceutical Basis of Therapeutics" (Eds. Hardman et al., Publ. McGraw Hill, NY) provides comprehensive guidance of useful drugs and their mechanisms of action. Medicated chewing gums have



been particularly effective in the delivery of agents such as nicotine as described in for example, U.S. Pat. No. 5,866, 179; and U.S. Pat. No. 5,889,028. U.S. Pat. No. 5,846,557 describes general chewing gum compositions containing cough suppressing agents. These patents are incorporated herein by reference as providing a teaching of the incorporation of medicinal agents into oral chewable formulations. It should be understood that the present chewing gum formulation(s) are not limited to the agents listed herein above, indeed any medicinal or other active agent that lends itself to ingestion may be formulated into the chewing gum formulations of the present invention.

Nutraceuticals and nutritional supplements may also be added to chewing gums as active agents. Among these are herbs and botanicals that include, but are not limited to capsicum, chamomile, cat's claw, echinacea, garlic, ginger, ginkgo, various ginseng, green tea, golden seal, kava kava, nettle, passion flower, saw palmetto, St. John's wort, and valerian. Also included are mineral supplements such as calcium, copper, iodine, iron, magnesium, manganese, molybdenum, phosphorous, selenium and zinc. Other nutraceuticals that also can be added to chewing gum as active agents are benzoin, fructo-oligosaccharides, glucosamine, grapeseed extract, guarana, inulin, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lecithin, lycopene, oligofructose, polyphenol and psyllium as well as weight loss agents such as chromium picolinate and phenylpropanolamine.

Preferably, the agents or medicaments are contained in the chewing gum formulation at levels of approximately 50 micrograms to 500 milligrams. The specific levels will depend on the active ingredient. For example, if chromium picolinate is the active ingredient in an embodiment, it would be present at a level of 50 micrograms per serving (2.8 grams stick of gum); aspirin would be preset at a level of 325 milligrams per 2.8/gram serving (stick).

The level of medicament or agent in the chewing gum formulation is selected so as to create, when the gum is chewed, a sufficiently high concentration of the medicament or agent in the saliva.

For example, when the agent is a stimulant such as nicotine or caffeine, the level of the stimulant in the chewing gum should be such that it creates a saliva content of stimulant of approximately 15 to 440 ppm when the chewing gum is chewed for 2 minutes. At this level, a sufficient amount of stimulant will be delivered to the chewer to create the effects set forth in the application. If a medicament is used such as a medicinal agent (e.g., analgesics), sufficient medicinal agent should be present in the chewing gum to create a saliva content of approximately 1700 to approximately 4400 ppm after the chewing gum has been chewed for 2 minutes. For botanical agents (e.g., chamomile, kava, kola, nut, ginseng, and Echinacea), the agent should be present in a sufficient amount to create a saliva content of approximately 85 to 1100 ppm when the chewing gum is chewed for 2 minutes. For a metabolizer, for example, chromium picolinate and hydroxy-chitic acid, the agents should be present in an amount to create a saliva content of approximately 0.5 to about 900 ppm when chewed for at least two minutes. If the agent is a vitamin or mineral (e.g., phosphatidylserine, vitamin C, and zinc), the agent should be present in the amount to create a saliva content of the vitamin or mineral of approximately 10 to about 250 ppm when chewed for 2 minutes.

Pursuant to the present invention, depending on the agent or medicament, the dosing regimen will change. For

example, if the medicament is an analgesic, the chewing gum would be taken on an as needed basis. Of course, similar to the oral administration of an analgesic, there would be restrictions on the number of pieces of chewing gum chewed, for example, not more often than one stick every four hours and not more often than four to five times a day. If the agent is a stimulant such as caffeine to be used to enhance performance than the chewing gum would be chewed, in a preferred embodiment ten minutes or less before the performance.

The medicament or agent can be contained in a variety of different chewing gum compositions. Referring now to the chewing gum, pursuant to the present invention, the chewing gum including the medicament or agent may be based on a variety of different chewing gums that are known. For example, the chewing gums can be low or high moisture, sugar or sugarless, wax containing or wax free, low calorie (via high base or low calorie bulking agents), and/or may contain dental agents.

Physical modifications of the active agent encapsulation with a highly water soluble substrate will increase its release in stick chewing gum as well as from the gum coating by increasing the solubility or dissolution rate. However, the active agent may also be encapsulated or entrapped to give a delayed release from stick chewing gum and from a gum coating. Any standard technique which gives partial or full encapsulation of the active agent can be used. These techniques include, but are not limited to, spray drying, spray chilling, fluid-bed coating and coacervation. These encapsulation techniques may be used individually in a single step process or in any combination in a multiple step process.

Active agents may be encapsulated with sweeteners, more specifically high-intensity sweeteners such as thaumatin, dihydrochalcones, acesulfame K, aspartame, N-substituted APM derivatives such as neotame, sucralose, alitame, saccharin and cyclamates. These can also have the effect of reducing unpleasant tastes such as bitterness. Additional bitterness inhibitors or taste maskers can also be combined with active agents and sweeteners to give a reduced unpleasant taste such as bitterness with delayed release active agent(s).

The encapsulation techniques described herein are standard coating techniques and generally give varying degrees of coating from partial to full coating, depending on the coating composition used in the process. Generally, compositions that have high organic solubility, good film-forming properties and low water solubility give better delayed release of active agents such as caffeine, while compositions that have high water solubility give better fast release. Such low water-solubility compositions include acrylic polymers and copolymers, carboxyvinyl polymer, polyamides, polystyrene, polyvinyl acetate, polyvinyl acetate phthalate, polyvinylpyrrolidone and waxes. Although all of these materials are possible for encapsulation of active agents such as caffeine, only food-grade materials should be considered. Two standard food-grade coating materials that are good film formers but not water soluble are shellac and Zein. Others which are more water soluble, but good film formers, are materials like agar, alginates, a wide range of cellulose derivatives like ethyl cellulose, methyl cellulose, sodium hydroxymethyl cellulose, and hydroxypropylmethyl cellulose, dextrin, gelatin, and modified starches. These ingredients, which are generally approved for food use, may give a fast release when used as an encapsulant. Other encapsulants like acacia or maltodextrin can also encapsulate active agent(s) and give a fast release rate in gum.

The amount of coating or encapsulating material on the active agent also may control the length of time for its

release from chewing gum. Generally, the higher the level of coating and the lower the amount of active agent, the slower the release during mastication with low water soluble compositions. The release rate is generally not instantaneous, but gradual over an extended period of time for stick gum. Delayed release allows the active agent to be masked in the mouth before being ingested, thus reducing bitterness or other unpleasant tastes. To obtain the delayed release, the encapsulant should be a minimum of about 20% of the coated active. Preferably, the encapsulant should be a minimum of about 30% of the coated active, and most preferably should be a minimum of about 40% of the coated active. Generally, water soluble encapsulating agents will increase the release rate of water insoluble active agents.

Another method of giving a modified release of active agent and the other agents described herein is agglomeration with agglomerating agent which partially coats the active agents. This method includes the step of mixing active agents and an agglomerating agent with a small amount of water or solvent. The mixture is prepared in such a way as to have individual wet particles in contact with each other so that a partial coating can be applied. After the water or other solvent is removed, the mixture is ground and used as a powdered active agent.

Materials that can be used as the agglomerating agent are the same as those used in encapsulation mentioned previously. Some of the better agglomerating agents for delayed release are the organic polymers like acrylic polymers and copolymers, polyvinyl acetate, polyvinylpyrrolidone, waxes, shellac and Zein. Other agglomerating agents are not as effective in giving a delayed release as are the polymers, waxes, shellac and Zein, but can be used to give some delayed release. Other agglomerating agents include, but are not limited to, agar, alginates, a wide range of water soluble cellulose derivatives like ethyl cellulose, methyl cellulose, sodium hydroxymethyl cellulose, hydroxypropylmethyl cellulose, dextrin, gelatin, modified starches, and vegetable gums like guar gum, locust bean gum and carrageenan. Even though the agglomerated active agent is only partially coated, when the quantity of coating is increased compared to the quantity of the active agent, the release can also be modified. The level of coating used in the agglomerated product is a minimum of about 5%. Preferably, the coating level is a minimum of about 15% and more preferably about 20%. Depending on the agglomerating agent, a higher or lower amount of agent may be needed to give the desired release of the active agent. Generally, water soluble agglomerants will increase the rate of release of water insoluble active agents.

Active agents may be coated in a two-step process or a multiple step process. Active agents may be encapsulated with any of the materials as described previously and then the encapsulated caffeine or other active agents can be agglomerated as previously described to obtain an encapsulated/agglomerated active agent product that could be used in chewing gum to give a delayed release of the active agent.

In another embodiment of this invention, active agent may be absorbed onto another component which is porous and becomes entrapped in the matrix of the porous component. Common materials used for absorbing active agents include, but are not limited to, silicas, silicates, pharماسorb clay, sponge-like beads or microbeads, amorphous carbonates and hydroxides, including aluminum and calcium lakes, all of which result in a delayed release of caffeine or other active agent.

Depending on the type of absorbent materials and how it is prepared, the amount of active agent that can be loaded

onto the absorbent will vary. Generally materials like polymers or sponge-like beads or microbeads, amorphous sugars and alditols and amorphous carbonates and hydroxides absorb about 10% to about 40% of the weight of the absorbent. Other materials like silicas and pharماسorb clays may be able to absorb about 20% to about 80% of the weight of the absorbent. Generally, water soluble absorbents will increase the release rate of water insoluble active agents.

The general procedure for absorbing active agent onto the absorbent is as follows. An absorbent like fumed silica powder can be mixed in a powder blender and a solution of active agent can be sprayed onto the powder as mixing continues. The aqueous solution can be about 1 to 2% solids, and higher solid levels to 15-30% may be used if temperatures up to 90° C. are used. Generally water is the solvent, but other solvents like alcohol could also be used if approved. As the powder mixes, the liquid is sprayed onto the powder. Spraying is stopped before the mix becomes damp. The still free-flowing powder is removed from the mixer and dried to remove the water or other solvent, and is then ground to a specific particle size.

After the active agent is absorbed or fixed onto an absorbent, the fixative/active agent can be coated by encapsulation. Either full or partial encapsulation may be used, depending on the coating composition used in the process. Full encapsulation may be obtained by coating with a polymer as in spray drying, spray chilling, fluid-bed coating, coacervation, or any other standard technique. A partial encapsulation or coating can be obtained by agglomeration of the fixative/active agent mixture using any of the materials discussed above.

Another form of encapsulation is by entrapment of an ingredient by fiber extrusion or fiber spinning into a polymer. Polymers that can be used for extrusion are PVAC, hydroxypropyl cellulose, polyethylene and other types of plastic polymers. A process of encapsulation by fiber extrusion is disclosed in U.S. Pat. No. 4,978,537, which is hereby incorporated by reference. The water insoluble polymer may be preblended with caffeine or other active agents prior to fiber extrusion, or may be added after the polymer is melted. As the extrudate is extruded, it results in small fibers that are cooled and ground. This type of encapsulation/entrapment generally gives a very long, delayed release of an active ingredient.

The four primary methods to obtain a treated active agent are: (1) encapsulation by spray drying, fluid-bed coating, spray chilling and coacervation to give full or partial encapsulation, (2) agglomeration to give partial encapsulation, (3) fixation or absorption which also gives partial encapsulation, and (4) entrapment into an extruded compound. These four methods, combined in any usable manner which physically modifies active agents dissolvability or modifies the release of active agents, are included in this invention.

Medicament actives may be combined in a chewing gum. In a stick gum, two, three, or more actives may be added to a single piece. One active could be encapsulated for fast release, another active for moderate release, and another active for slow release. In addition, a single medicament active could be encapsulated and entrapped to release at various times as the gum is being chewed. This type of gum formulation could be effective for time release medication.

Medicament actives may also be combined in a coated chewing gum product. A single active may be added to a gum coating for fast release and also added to the gum center with or without encapsulation for slow release. If the active



has an affinity for the gum base it may naturally give a slow release without encapsulation. If the active is fast release it would have to be encapsulated or entrapped for the desired time release.

A combination of medicament actives may be used in the gum coating and in the gum center for various reasons. In some cases, medicaments may be reactive to one another and should be kept from coming in contact with each other. In other cases, combinations of medicaments may be used for various symptoms where multiple medicaments may be effective. For example, a decongestant such as pseudoephedrine may be added to a gum coating and an antihistamine such as chlorpheniramine may be added to a gum center to treat cold/allergy symptoms. For sore throat, an oral anesthetic like dyclonine hydrochloride may be used in the gum coating and an antibacterial agent like cetyl pyridinium chloride may be added to a gum center. Additionally, any other materials like dextromethorphan hydrobromide for cough relief or an analgesic like ketoprofen may be added to either a gum coating and a gum center for cold symptoms. Other combinations of medicament active agents for other types of ailments are also within the scope of this invention.

In many instances a medicament may have a bitter taste. If the medicament were added to a coating at a very low level, it would still have the effect of fast release initially. In this case, the active agent may be added to the gum coating at a very low level beneath its taste threshold. Additional active agent that is encapsulated and entrapped may then be added to the gum center for slow release. This bitter active agent can then be kept below its taste threshold level and release slowly as the gum is being chewed, but the active agent would continue to be released to give its effective dosage.

In many instances, active medicaments may have a low quality off-taste or bitterness, especially if added to a chewing gum coating. In most cases, this off taste may be masked with high intensity sweeteners, but in other instances, a bitterness inhibitor may be needed to reduce a bitter taste of a medicament.

There are a wide variety of bitterness inhibitors that can be used in food products as well as with active agents. Some of the preferred bitterness inhibitors are the sodium salts which are discussed in the article *Suppression of Bitterness by Sodium: Variations Among Bitter Taste Stimuli*, by R. A. S. Breslin and G. K. Beceuchep from Monell Chemical Senses Center, Philadelphia, Pa. Sodium salts discussed are sodium acetate and sodium gluconate. Other sodium salts that may also be effective are sodium glycinate, sodium ascorbate and sodium glycerolphosphate. Among these, the most preferred is sodium gluconate and sodium glycinate since they have a low salty taste and are most effective to reduce bitterness of most active medicaments.

Most of the sodium salts are very water soluble and are readily released from chewing gum to function as bitterness inhibitors. In most instances, the sodium salts which release readily from chewing gum may be modified by encapsulation to give an even faster release from chewing gum. However, in some instances the sodium salts would be encapsulated or entrapped to give a delayed release from gum. Generally, the bitterness inhibitor should release with the active medicament for maximum effectiveness.

In addition to physically modifying the active medicament for fast or delayed release, medicaments may be dissolved in solvents, flavors, or other transdermal vehicles used as absorption enhancing agents and added to gum or to a gum coating. The absorption enhancing agents may also be

added to the gum or gum coating separately from the active ingredient. Their presence may help volatilize medicaments or allow increased buccal/lingual absorption of the active agent through the nasal mucosal or the lungs. These solvents, flavors, or transdermal vehicles may transport medicaments faster through the oral mucosa.

Faster absorption may be affected by increasing flavor levels as well as the addition of other flavor components, such as menthol and menthol derivatives, limonene, carvone, isomenthol, eucalyptol, menthone, pynene, camphor and camphor derivatives, as well as monoterpene natural products, monoterpene derivatives, and sesquiterpenes, including caryophyllene and copaene. Other vehicles that may be used to increase transdermal absorption are: ethanol, polyethylene glycol, 2-pyrrolidones, myristic acid, Brij-35 (surfactant), p-phenyl phenol, nitrobenzene, stearyl alcohol, cetyl alcohol, croton oil, liquid paraffin, dimethyl sulfoxide (DMSO), non-ionic surfactants, liposomes, lecithin fractions, and long chain amphipathic molecules (molecules with polar or non-ionized groups on one end and non-polar groups at the other end).

In addition, some polysaccharides such as cellulose gums, natural gums like guar gum, gum arabic, and others may be mixed with active medicaments or mixed in the gum formulation with the medicament. This may allow the medicaments to stick to the surface of the oral mucosa during chewing and increase oral absorption. Bioadhesives may act in a similar manner to achieve increased absorption of the active medicament.

In some instances the gum formulation may have an effect on release rate of the medicament. Water miscible medicaments may be released more slowly when using a highly hydrophillic gum base and more quickly from a lipophillic gum base. On the other hand, oil miscible medicaments may release more quickly when using a highly hydrophillic gum base and more slowly from a lipophillic gum base. Also medicaments may release more quickly by using high HLB solubilizers in the gum formulation. Medicaments may also be emulsified together with water soluble bulking agents to increase release of the medicaments.

Other gum formula modifications may also affect the release rate of medicaments. Texture modifiers to soften base may give faster release where hard bases may give slower release. Addition of alkaline materials such as sodium bicarbonate or sodium hydroxide may make the saliva slightly alkaline, which may increase buccal/lingual absorption of the medicament into the bloodstream. Use of a buffer in the gum formula may affect release rate or absorption or shelf life of certain medicaments or supplements. Gum base made with talc may offer unique release and shelf life improvements. Other additives, such as astringents may give the sensation of dry mouth, which may improve medicament absorption. Also, some types of hot, spicy flavors such as ginger or hot pepper may give the impression of high activity of the medicament.

Medicaments may be added to chewing gum via special carriers which may affect the release rate and its absorption. Some carriers that may be used are activated charcoal, molecular sieves, corn starch granules, microsponges, or liposomes. The medicament may be sugar or polyol candy coated, or entrapped in cyclodextrin for fast release to dissolve quickly in the mouth during chewing.

Release of the medicament from gum may also be effected by particle size of the coated medicament. Small particles release more quickly whereas large particles more slowly. Fast release can also be accomplished by dissolving medi-

cament in a liquid and used in a liquid center gum. Some medicaments may be advantageous to use in both slow and fast release. Quick release may give good oral absorption, then slow release may result by swallowing the cud. This may be particularly effective if a biodegradable gum base is used. On the other hand, some medicaments may have an advantage with a slow initial release, but increases later. This can reduce side effects of the medicament and improve adaptation to the medicament. Slow release may also be accomplished by attaching a medicament to a polymer used in the chewing gum.

Release of a medicament or active agent may also be effected by the shape and size of the chewing gum product. Flat stick pieces of gum with large surface area may release actives faster into saliva from gum when chewed, whereas round or cube pieces may release medicaments and actives more slowly. Gum formulations, especially those that are anhydrous or have no gum softening agents may be ground to a powder. This powder may be dusted onto the surface of another gum formulation or coated onto a ball or pillow shape gum product. This powder may also be tableted in a tablet press to give a unique form to be chewed for release of its active agent. Other forms of gum to be used are rolled sticks, or soft squeezable gum from a tube.

Active medicaments can also be added to chewing gum formulations that are made into tablets. Tableting of chewing gum is disclosed in U.K. Patent Publication No. 1,489,832; U.S. Pat. No. 4,753,805; EP Patent Publication No. 0 221 850; and Italy Patent Publication No. 1,273,487. These patents disclose active agents added to chewing gum which is then tableted. As an embodiment of this invention, active agents may be encapsulated or entrapped and added to a chewing gum formulation which is then tableted. In addition, a formed chewing gum tablet may also be used as a core for a coated chewing gum pellet that is coated with a sugar, polyol or film. The chewing gum core may contain one active agent or multiple active medicaments and the coating may contain one or more active medicaments. This form will yield unique chewing gum products.

The previously described encapsulated, agglomerated or absorbed active agent may readily be added to a chewing gum composition. The remainder of the chewing gum ingredients are well known to those of skill in the art and are not intended to be limiting to the present invention. That is, the treated particles of active agent can be added to conventional chewing gum formulations in a conventional manner. Treated active agent may be added to a sugar chewing gum or a sugarless chewing gum.

In general, a chewing gum composition typically comprises a water-soluble bulk portion, a water-insoluble chewable grams base portion and typically water-insoluble flavoring agents. The water-soluble portion dissipates with a portion of the flavoring agent over a period of time during chewing. The gum base portion is retained in the mouth throughout the chew.

The insoluble gum base generally comprises elastomers, resins, fats and oils, softeners and inorganic fillers. The gum base may or may not include wax. The insoluble gum base can constitute approximately 5% to about 95% by weight of the chewing gum, more commonly the gum base comprises 10% to about 50% of the gum, and in some preferred embodiments approximately 25% to about 35% by weight, of the chewing gum.

In a particular embodiment, the chewing gum base of the present invention contains about 20% to about 60% by weight synthetic elastomer, about 0% to about 30% by

weight natural elastomer, about 5% to about 55% by weight elastomer plasticizer, about 4% to about 35% by weight filler, about 5% to about 35% by weight softener, and optional minor amounts (about 1% or less by weight) of miscellaneous ingredients such as colorants, antioxidants, etc.

Synthetic elastomers may include, but are not limited to, polyisobutylene with GPC weight average molecular weight of about 10,000 to about 95,000, isobutylene-isoprene copolymer (butyl elastomer), styrene-butadiene, copolymers having styrene-butadiene ratios of about 1:3 to about 3:1, polyvinyl acetate having GPC weight average molecular weight of about 2,000 to about 90,000, polyisoprene, polyethylene, vinyl acetate-vinyl laurate copolymer having vinyl laurate content of about 5% to about 50% by weight of the copolymer, and combinations thereof.

Preferred ranges for polyisobutylene are 50,000 to 80,000 GPC weight average molecular weight and for styrene-butadiene are 1:1 to 1:3 bound styrene-butadiene, for polyvinyl acetate are 10,000 to 65,000 GPC weight average molecular weight with the higher molecular weight polyvinyl acetates typically used in bubble gum base, and for vinyl acetate-vinyl laurate, vinyl laurate content of 10-45%.

Natural elastomers may include natural rubber such as smoked or liquid latex and guayule as well as natural gums such as jelutong, lechi caspi, perillo, sorva, massaranduba balata, massaranduba chocolate, nispero, rosindinha, chicle, gutta hang kang, and combinations thereof. The preferred synthetic elastomer and natural elastomer concentrations vary depending on whether the chewing gum in which the base is used is adhesive or conventional, bubble gum or regular gum, as discussed below. Preferred natural elastomers include jelutong, chicle, sorva and massaranduba balata.

Elastomer plasticizers may include, but are not limited to, natural rosin esters such as glycerol esters or partially hydrogenated rosin, glycerol esters of polymerized rosin, glycerol esters of partially dimerized rosin, glycerol esters of rosin, pentaerythritol esters of partially hydrogenated rosin, methyl and partially hydrogenated methyl esters of rosin, pentaerythritol esters of rosin; synthetics such as terpene resins derived from alpha-pinene, beta-pinene, and/or d-limonene; and any suitable combinations of the foregoing. The preferred elastomer plasticizers will also vary depending on the specific application, and on the type of elastomer which is used.

Fillers/texturizers may include magnesium and calcium carbonate, ground limestone, silicate types such as magnesium and aluminum silicate, clay, alumina, talc, titanium oxide, mono-, di- and tri-calcium phosphate, cellulose polymers, such as wood, and combinations thereof.

Softeners/emulsifiers may include tallow, hydrogenated tallow, hydrogenated and partially hydrogenated vegetable oils, cocoa butter, glycerol monostearate, glycerol triacetate, lecithin, mono-, di- and triglycerides, acetylated monoglycerides, fatty acids (e.g. stearic, palmitic, oleic and linoleic acids), and combinations thereof.

Colorants and whiteners may include FD&C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide, and combinations thereof.

The base may or may not include wax. An example of a wax-free gum base is disclosed in U.S. Pat. No. 5,286,500, the disclosure of which is incorporated herein by reference.

In addition to a water insoluble gum base portion, a typical chewing gum composition includes a water soluble bulk portion and one or more flavoring agents. The water

soluble portion can include bulk sweeteners, high intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, acidulants, fillers, antioxidants, and other components that provide desired attributes.

Softeners are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. The softeners, which are also known as plasticizers and plasticizing agents, generally constitute between approximately 0.5% to about 15% by weight of the chewing gum. The softeners may include glycerin, lecithin, and combinations thereof. Aqueous sweetener solutions such as those containing sorbitol, hydrogenated starch hydrolysates, corn syrup and combinations thereof, may also be used as softeners and binding agents in chewing gum.

Bulk sweeteners include both sugar and sugarless components. Bulk sweeteners typically constitute about 5% to about 95% by weight of the chewing gum, more typically, about 20% to about 80% by weight, and more commonly, about 30% to about 60% by weight of the gum. Sugar sweeteners generally include saccharide-containing components commonly known in the chewing gum art, including but not limited to, sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, levulose, galactose, corn syrup solids, and the like, alone or in combination. Sugarless sweeteners include, but are not limited to, sugar alcohols such as sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates, maltitol, and the like, alone or in combination.

High intensity artificial sweeteners can also be used, alone or in combination, with the above. Preferred sweeteners include, but are not limited to, sucralose, aspartame, N-substituted APM derivatives such as neotame, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizinate, dihydrochalcones, thaumatin, monellin, and the like, alone or in combination. In order to provide longer lasting sweetness and flavor perception, it may be desirable to encapsulate or otherwise control the release of at least a portion of the artificial sweetener. Such techniques as wet granulation, wax granulation, spray drying, spray chilling, fluid bed coating, coacervation, and fiber extension may be used to achieve the desired release characteristics.

Combinations of sugar and/or sugarless sweeteners may be used in chewing gum. Additionally, the softener may also provide additional sweetness such as with aqueous sugar or alditol solutions.

If a low calorie gum is desired, a low caloric bulking agent can be used. Examples of low caloric bulking agents include: polydextrose; Raftilose, Raftilin; Fructooligosaccharides (NutraFlora); Palatinose oligosaccharide; Guar Gum Hydrolysate (Sun Fiber); or indigestible dextrin (Fibersol). However, other low calorie bulking agents can be used.

A variety of flavoring agents can also be used, if desired. The flavor can be used in amounts of about 0.1 to about 15 weight percent of the gum, and preferably, about 0.2% to about 5% by weight. Flavoring agents may include essential oils, synthetic flavors or mixtures thereof including, but not limited to, oils derived from plants and fruits such as citrus oils, fruit essences, peppermint oil, spearmint oil, other mint oils, clove oil, oil of wintergreen, anise and the like. Artificial flavoring agents and components may also be used. Natural and artificial flavoring agents may be combined in any sensorially acceptable fashion.

If the medicament or active is water soluble in the chewing gum, it preferably will include a base/emulsifier system which leads to the desired concentration of the

medicament in the saliva (more hydrophilic balance). If the medicament or active is water insoluble, the chewing gum preferably includes a base/emulsifier system which leads to the desired concentration of the medicament in the saliva (more lipophilic balance).

In manufacturing the chewing gum including the active agent or ingredient, the active agent or medicament is added, preferably, early on in the mix. The smaller the amount of active ingredient used, the more necessary it becomes to preblend that particular ingredient to assume uniform distribution throughout the batch of gum. Whether a preblend is used or not, the active agent or medicament should be added within the first five minutes of mixing. For faster release, the active agent may be added late in the process.

In general, chewing gum is manufactured by sequentially adding the various chewing gum ingredients to a commercially available mixer known in the art. After the ingredients have been thoroughly mixed, the gum mass is discharged from the mixer and shaped into the desired form such as rolling sheets and cutting into sticks, extruding into chunks or casting into pellets, which are then coated or panned.

Generally, the ingredients are mixed by first melting the gum base and adding it to the running mixer. The base may also be melted in the mixer itself. Color or emulsifiers may also be added at this time. A softener such as glycerin may also be added at this time, along with syrup and a portion of the bulking agent. Further parts of the bulking agent are added to the mixer. Flavoring agents are typically added with the final portion of the bulking agent. Other optional ingredients are added to the batch in a typical fashion, well known to those of ordinary skill in the art.

The entire mixing procedure typically takes from five to fifteen minutes, but longer mixing times may sometimes be required. Those skilled in the art will recognize that many variations of the above described procedure may be followed.

Chewing gum base and chewing gum product have been manufactured conventionally using separate mixers, different mixing technologies and, often, at different factories. One reason for this is that the optimum conditions for manufacturing gum base, and for manufacturing chewing gum from gum base and other ingredients such as sweeteners and flavors, are so different that it has been impractical to integrate both tasks. Chewing gum base manufacture, on the one hand, involves the dispersive (often high shear) mixing of difficult-to-blend ingredients such as elastomer, filler, elastomer plasticizer, base softeners/emulsifiers and sometimes wax, and typically requires long mixing times. Chewing gum product manufacture, on the other hand, involves combining the gum base with more delicate ingredients such as product softeners, bulk sweeteners, high intensity sweeteners and flavoring agents using distributive (generally lower shear) mixing, for shorter periods.

In order to improve the efficiency of gum base and gum product manufacture, there has been a trend toward the continuous manufacture of gum bases and products. U.S. Pat. No. 3,995,064, issued to Ehrigott et al., discloses the continuous manufacture of gum base using a sequence of mixers or a single variable mixer. U.S. Pat. No. 4,459,311, issued to DeTora et al., also discloses the continuous manufacture of gum base using a sequence of mixers. Other continuous gum base manufacturing processes are disclosed in European Publication No. 0,273,809 (General Foods France) and in French Publication No. 2,635,441 (General Foods France).

U.S. Pat. No. 5,045,325, issued to Lesko et al., and U.S. Pat. No. 4,555,407, issued to Kramer et al., disclose pro-

cesses for the continuous production of chewing gum products. In each case, however, the gum base is initially prepared separately and is simply added into the process. U.S. Pat. No. 4,968,511, issued to D'Amelia et al., discloses a chewing gum product containing certain vinyl polymers which can be produced in a direct one-step process not requiring separate manufacture of gum base.

Active medicaments may also be added to chewing gum products made by a continuous process. U.S. Pat. Nos. 5,543,160 and 5,800,847 disclose a continuous process using a single extruder to make the gum base and the gum product. U.S. Pat. Nos. 5,397,580 and 5,523,097 disclose a continuous process using two or more extruders for base and chewing gum mixing. U.S. Pat. Nos. 5,419,919 and 5,571,543 disclose a continuous process using a paddle type mixer which has low pressure and high residence time for adequate mixing.

Active medicaments, whether encapsulated, entrapped or not, can be added at any time during the continuous mixing process. Generally, actives would probably be added in the gum mixing sections. Specific advantages to adding active medicaments to a continuous process of manufacturing gum are that more thorough mixing is accomplished in this type of process with lower amount of residence time of the active agent at high temperatures during processing. The enclosed system used in continuous processing can result in more thorough mixing, better reproducibility of the amount of active within the gum matrix, and less loss in the amount of the active medicament.

Another method of treating the medicament or active agent is to physically isolate the active agent from other chewing gum ingredients to effect its release rate and stability. The active agent may be added to the liquid inside a liquid center gum product. The center fill of gum product may comprise one or more carbohydrate syrups, glycerin, thickeners, flavors, acidulants, colors, sugars and sugar alcohols in conventional amounts. The ingredients are combined in a conventional manner. The total amount of active agent may be dissolved in the center-fill liquid. This method of using active agent in chewing gum may give a more controlled release rate, and may reduce or eliminate any possible reaction with gum base, flavor components, or other components, yielding improved shelf stability. A liquid-center gum may also be coated with a sugar, polyol or film to yield a unique chewing gum product.

Another method of isolating medicaments or active agents from other chewing gum ingredients is to add active agents to the dusting compound of a chewing gum. A rolling or dusting compound serves to reduce sticking to machinery as it is wrapped, and sticking to its wrapper after it is wrapped and being stored. The rolling compound comprises active agents in combination with mannitol, sorbitol, sucrose, starch, calcium carbonate, talc, other orally acceptable substances or a combination thereof. The rolling compound constitutes from about 0.25% to about 10.0% or about 1% to about 3% of weight of the chewing gum composition. This method of using active agents in the chewing gum can allow a lower usage level, can give a more controlled release rate, and can reduce or eliminate any possible reaction with the gum base, flavor components, or other components, yielding improved self stability.

Another method of isolating medicament or active agents is to use it in the coating/panning of a pellet chewing gum. Pellet or ball gum is prepared as conventional chewing gum but formed into pellets that are pillow shaped, or into balls. The pellets/balls can be then sugar coated or panned by

conventional panning techniques to make a unique coated pellet gum. The active agent may be soluble in flavor or can be blended with other powders often used in some types of conventional panning procedures. Active agents are isolated from other gum ingredients which modifies its release rate from chewing gum. Levels of actives may be about 10 ppm to 5% by weight of chewing gum coating. The weight of the coating may be about 20% to about 50% of the weight of the finished product, but may be as much as 75% of the total gum product.

Conventional panning procedures generally coat with sucrose, but recent advances in panning have allowed use of other carbohydrate materials to be used in place of sucrose. Some of these components include, but are not limited to, dextrose, maltose, palatinose, xylitol, lactitol, hydrogenated isomaltulose, erythritol maltitol, and other new alditols or combinations thereof. These materials may be blended with panning modifiers including, but not limited to, gum arabic, maltodextrins, corn syrup, gelatin, cellulose type materials like carboxymethyl cellulose or hydroxymethyl cellulose, starch and modified starches, vegetables gums like alginates, locust bean gum, guar gum, and gum tragacanth, insoluble carbonates like calcium carbonate or magnesium carbonate and talc. Antitack agents may also be added as panning modifiers, which allow the use of a variety of carbohydrates and sugar alcohols to be used in the development of new panned or coated gum products. Flavors may also be added with the sugar or sugarless coating and with the active to yield unique product characteristics.

Another type of pan coating could also isolate the active agent from the chewing gum ingredients. This technique is referred to as a film coating and is more common for pharmaceuticals than in chewing gum, but procedures are similar. A film like shellac, zein, or cellulose type material is applied onto a pellet-type product forming a thin film on the surface of the product. The film is applied by mixing the polymer, plasticizer and a solvent (pigments are optional) and spraying the mixture onto the pellet surface. This is done in conventional type panning equipment, or in more advanced side-vented coating pans. Since most active agents may be alcohol soluble, they may be readily added with this type of film. When a solvent like an alcohol is used, extra precautions are needed to prevent fires and explosions, and specialized equipment must be used.

Some film polymers can use water as the solvent in film coating. Recent advances in polymer research and in film coating technology eliminates the problem associated with the use of solvents in coating. These advances make it possible to apply aqueous films to a pellet or chewing gum product. Some active agents can be added to this aqueous film or even the alcohol solvent film, in which an active agent is highly soluble. This film may also contain a flavor along with a polymer and plasticizer. The active agent can also be dissolved in the aqueous solvent and coated on the surface with the aqueous film. This will give a unique sweetness release to a film-coated product.

After a coating film with an active medicament is applied to a chewing gum product, a hard shell sugar or polyol coating may then be applied over the film coated product. In some instances a soft shell sugar or polyol coating may also be used over the film coated product. The level of film coating applied to a pellet gum may be generally about 0.5% to about 3% of the gum product. The level of overcoating of the hard or soft shell may be about 20% to about 60%. When the active agent is added with the film coating and not with the sugar/polyol coating, better control of the amount of active agent in the product may be obtained. In addition, the

sugar/polyol overcoating may give an improved stability to the active agent in the product.

As noted above, the coating may contain ingredients such as flavoring agents, as well as artificial sweeteners and dispersing agents, coloring agents, film formers and binding agents. Flavoring agents contemplated by the present invention include those commonly known in the art such as essential oils, synthetic flavors or mixtures thereof, including but not limited to oils derived from plants and fruits such as citrus oils, fruit essences, peppermint oil, spearmint oil, other mint oils, clove oil, oil of wintergreen, anise and the like. The flavoring agents may be used in an amount such that the coating will contain from about 0.2% to about 3% flavoring agent, and preferably from about 0.7% to about 2.0% flavoring agent.

Artificial sweeteners contemplated for use in the coating include but are not limited to synthetic substances, saccharin, thaumatin, alitame, saccharin salts, aspartame, N-substituted APM derivatives such as neotame, sucralose and acesulfame-K. The artificial sweetener may be added to the coating syrup in an amount such that the coating will contain from about 0.01% to about 0.5%, and preferably from about 0.1% to about 0.3% artificial sweetener.

Dispersing agents are often added to syrup coatings for the purpose of whitening and tack reduction. Dispersing agents contemplated by the present invention to be employed in the coating syrup include titanium dioxide, talc, or any other antistick compound. Titanium dioxide is a presently preferred dispersing agent of the present invention. The dispersing agent may be added to the coating syrup in amounts such that the coating will contain from about 0.1% to about 1.0%, and preferably from about 0.3% to about 0.6% of the agent.

Coloring agents are preferably added directly to the syrup in the dye or lake form. Coloring agents contemplated by the present invention include food quality dyes. Film formers preferably added to the syrup include methyl cellulose, gelatins, hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose and the like and combinations thereof. Binding agents may be added either as an initial coating on the chewing gum center or may be added directly into the syrup. Binding agents contemplated by the present invention include gum arabic, gum talha (another type of acacia), alginate, cellulose, vegetable gums and the like.

The coating is initially present as a liquid syrup which contains from about 30% to about 80% or 85% of the coating ingredients previously described herein, and from about 15% or 20% to about 70% of a solvent such as water. In general, the coating process is carried out in a rotating pan. Sugar or sugarless gum center tablets to be coated are placed into the rotating pan to form a moving mass.

The material or syrup which will eventually form the coating is applied or distributed over the gum center tablets. Flavoring agents may be added before, during and after applying the syrup to the gum centers. Once the coating has dried to form a hard surface, additional syrup additions can be made to produce a plurality of coatings or multiple layers of hard coating.

In a hard coating panning procedure, syrup is added to the gum center tablets at a temperature range of from about 100° F. to about 240° F. Preferably, the syrup temperature is from about 130° F. to about 200° F. throughout the process in order to prevent the polyol or sugar in the syrup from crystallizing. The syrup may be mixed with, sprayed upon, poured over, or added to the gum center tablets in any way known to those skilled in the art.

In general, a plurality of layers is obtained by applying single coats, allowing the layers to dry, and then repeating the process. The amount of solids added by each coating step depends chiefly on the concentration of the coating syrup. Any number of coats may be applied to the gum center tablet. Preferably, no more than about 75-100 coats are applied to the gum center tablets. The present invention contemplates applying an amount of syrup sufficient to yield a coated comestible containing about 10% to about 65% coating. Where higher dosage of an active agent is needed, the final product may be higher than 65% coating.

Those skilled in the art will recognize that in order to obtain a plurality of coated layers, a plurality of premeasured aliquots of coating syrup may be applied to the gum center tablets. It is contemplated, however, that the volume of aliquots of syrup applied to the gum center tablets may vary throughout the coating procedure.

Once a coating of syrup is applied to the gum center tablets, the present invention contemplates drying the wet syrup in an inert medium. A preferred drying medium comprises air. Preferably, forced drying air contacts the wet syrup coating in a temperature range of from about 70° to about 115° F. More preferably, the drying air is in the temperature range of from about 80 to about 100° F. The invention also contemplates that the drying air possess a relative humidity of less than about 15 percent. Preferably, the relative humidity of the drying air is less than about 8 percent.

The drying air may be passed over and admixed with the syrup coated gum centers in any way commonly known in the art. Preferably, the drying air is blown over and around or through the bed of the syrup coated gum centers at a flow rate, for large scale operations, of about 2800 cubic feet per minute. If lower quantities of material are being processed, or if smaller equipment is used, lower flow rates would be used.

For many years, flavors have been added to a sugar coating of pellet gum to enhance the overall flavor of gum. These flavors include spearmint flavor, peppermint flavor, wintergreen flavor, and fruit flavors. These flavors are generally preblended with the coating syrup just prior to applying it to the core or added together to the core in one or more coating applications in a revolving pan containing the cores. Generally, the coating syrup is very hot, about 130° to 200° F., and the flavor may volatilize if preblended with the coating syrup too early.

The concentrated coating syrup is applied to the gum cores as a hot liquid, the sugar or polyol allowed to crystallize, and the coating then dried with warm, dry air. This is repeated in about 30 to 80 applications to obtain a hard shell coated product having an increased weight gain of about 40% to 75%. A flavor is applied with one, two, three or even four or more of these coating applications. Each time flavor is added, several non-flavored coatings are applied to cover the flavor before the next flavor coat is applied. This reduces volatilization of the flavor during the coating process.

For mint flavors such as spearmint, peppermint and wintergreen, some of the flavor components are volatilized, but sufficient flavor remains to give a product having a strong, high impact flavor. Fruit flavors, that may contain esters, are more easily volatilized and may be flammable and/or explosive and therefore, generally these type of fruit flavors are not used in coatings.

In an embodiment of this invention, an active agent is preblended with a gum arabic solution to become a paste and



then applied to the cores. To reduce stickiness, the preblend may be mixed with a small amount of coating syrup before being applied. Forced air drying is then continued as the gum arabic binds the active agent to the cores. Then additional coatings are applied to cover the active agent and imbed the treated active agent in the coatings.

#### Gum Formulation Examples

The following examples of the invention and comparative examples are provided by way of explanation and illustration.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas for pellet centers are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

Keeping this in mind, if a coating of about 25% of the total product is added to a pellet core as sugar or polyols, the gum base in the pellet core should also be increased by 25%. Likewise, if a 33% coating is applied, the base levels should also be increased by 33%. As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Even higher levels of base may be used if an active is added to a pellet coating. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

A wide range of changes and modifications to the embodiments of the invention described above will be apparent to persons skilled in the art. For example, while the invention is described with respect to hard-coated chewing gum, it will be appreciated that the process is applicable to coating other food products, such as candies, in which a coating with dyclonine hydrochloride would have utility.

#### EXAMPLES

The following examples of the invention and comparative examples are provided by way of explanation and illustration.

The formulas listed in Table 1 comprise various sugar-type formulas in which active medicament can be added to gum after it is dissolved in water or mixed with various aqueous solvents. Dyclonine hydrochloride is an active medicament used as an oral anesthetic for sore throat. These formulas give a 3 gram stick with 3 mg of dyclonine hydrochloride.

TABLE 1

|                    | (WEIGHT PERCENT) |       |       |       |       |       |       |       |
|--------------------|------------------|-------|-------|-------|-------|-------|-------|-------|
|                    | EX. 1            | EX. 2 | EX. 3 | EX. 4 | EX. 5 | EX. 6 | EX. 7 | EX. 8 |
| SUGAR              | 62.5             | 64.6  | 63.6  | 65.0  | 65.0  | 63.0  | 61.6  | 47.0  |
| BASE               | 19.2             | 19.2  | 19.2  | 19.2  | 19.2  | 19.2  | 19.2  | 19.2  |
| CORN SYRUP         | 15.9             | 12.9  | 12.9  | 12.9  | 12.9  | 15.9  | 0.0   | 2.9   |
| PEPPER-MINT FLAVOR | 0.9              | 0.9   | 0.9   | 0.9   | 0.9   | 0.0   | 0.9   | 0.9   |
| GLYCERIN           | 1.4              | 1.4   | 1.4   | 0.0   | 0.0   | 0.9   | 1.4   | 0.0   |

TABLE 1-continued

|                     | (WEIGHT PERCENT) |       |       |       |       |       |       |       |
|---------------------|------------------|-------|-------|-------|-------|-------|-------|-------|
|                     | EX. 1            | EX. 2 | EX. 3 | EX. 4 | EX. 5 | EX. 6 | EX. 7 | EX. 8 |
| LIQUID/ACTIVE BLEND | 0.1              | 1.0   | 2.0   | 2.0   | 2.0   | 1.0   | 16.9  | 30.0  |

#### Example 1

Dyclonine hydrochloride powder can be added directly to the gum.

#### Example 2

A 1 gram quantity of dyclonine hydrochloride can be dissolved in 9 grams of water giving a 10% solution and added to gum.

#### Example 3

A 1 gram quantity of dyclonine hydrochloride can be dissolved in 9 grams of water and mixed with 10 grams of glycerin and added to the gum.

#### Example 4

A 1 gram quantity of dyclonine hydrochloride is mixed with 19 grams of glycerin giving a 5% solution and added to gum.

#### Example 5

A 1 gram quantity of dyclonine hydrochloride is mixed with 19 grams of propylene glycol giving a 5% solution and added to gum.

#### Example 6

A 1 gram quantity of dyclonine hydrochloride is dissolved in 9 grams of ethanol, which is then mixed with 90 grams of peppermint flavor and added to gum.

#### Example 7

A 1 gram quantity of dyclonine hydrochloride is dissolved in 168 grams of corn syrup and added to chewing gum.

#### Example 8

To a 200 gram quantity of corn syrup is added 100 grams of glycerin. To this mixture is added 1 gram of dyclonine hydrochloride and blended. This mixture is then added to gum.

In the next examples of sugar formulations, dyclonine hydrochloride can be dissolved in water and emulsifiers can be added to the aqueous solution. Example solutions can be prepared by dissolving 10 grams of dyclonine hydrochloride in 75 grams of water and adding 15 grams of emulsifiers of various hydrophilic-lipophilic balance (HLB) values to the solution. The mixtures can then be used in the following formulas. Example 9 uses a mixture of dyclonine hydrochloride and water with no emulsifier. The HLB value of the emulsifiers used in Examples 10-14 are listed in Table 2.

TABLE 2

| (WEIGHT PERCENT)                |       |         |         |         |         |          |
|---------------------------------|-------|---------|---------|---------|---------|----------|
|                                 | EX. 9 | EX. 10  | EX. 11  | EX. 12  | EX. 13  | EX. 14   |
| SUGAR                           | 54.7  | 54.7    | 54.7    | 54.7    | 54.7    | 54.7     |
| BASE                            | 19.2  | 19.2    | 19.2    | 19.2    | 19.2    | 19.2     |
| CORN SYRUP                      | 12.9  | 12.9    | 12.9    | 12.9    | 12.9    | 12.9     |
| GLYCERIN                        | 1.4   | 1.4     | 1.4     | 1.4     | 1.4     | 1.4      |
| DEXTROSE                        | 9.9   | 9.9     | 9.9     | 9.9     | 9.9     | 9.9      |
| MONO-<br>HYDRATE                |       |         |         |         |         |          |
| PEPP. FLAVOR                    | 0.9   | 0.9     | 0.9     | 0.9     | 0.9     | 0.9      |
| ACTIVE AGENT                    | 1.0   | 1.0     | 1.0     | 1.0     | 1.0     | 1.0      |
| EMULSIFIER/<br>WATER<br>MIXTURE |       |         |         |         |         |          |
|                                 | None  | HLB = 2 | HLB = 4 | HLB = 6 | HLB = 9 | HLB = 12 |

## Examples 15-20

The same as the formulations made in Examples 9-14, respectively, except that the flavor can be mixed together with the aqueous dyclonine hydrochloride solution and emulsified before adding the mixture to the gum batch.

The following Tables 3 through 10 are examples of gum formulations that demonstrate formula variations in which dyclonine hydrochloride may be used. The active agent may be added with or without encapsulation, or may be treated for fast release.

Examples 21-24 in Table 3 demonstrates the use of dyclonine hydrochloride in low-moisture sugar formulations showing less than 2% theoretical moisture:

TABLE 3

| (WEIGHT PERCENT)                |        |        |        |        |
|---------------------------------|--------|--------|--------|--------|
|                                 | EX. 21 | EX. 22 | EX. 23 | EX. 24 |
| SUGAR                           | 58.8   | 58.6   | 58.8   | 54.6   |
| GUM BASE                        | 19.2   | 19.2   | 19.2   | 19.2   |
| CORN <sup>a</sup><br>SYRUP      | 6.0    | 6.0    | —      | —      |
| DEXTROSE                        | 10.0   | 10.0   | 10.0   | 10.0   |
| MONOHY-<br>DRATE                |        |        |        |        |
| LACTOSE                         | 0.0    | 0.0    | 0.0    | 5.0    |
| GLYCERIN <sup>b</sup>           | 5.0    | 5.0    | 11.0   | 10.0   |
| FLAVOR                          | 0.9    | 0.9    | 0.9    | 0.9    |
| ACTIVE                          | 0.1    | 0.3    | 0.1    | 0.3    |
| DYCLONINE<br>HYDRO-<br>CHLORIDE |        |        |        |        |

<sup>a</sup>Corn syrup is evaporated to 85% solids, 15% moisture

<sup>b</sup>Glycerin and syrup may be blended and co-evaporated

Examples 25-28 in Table 4 demonstrate the use of dyclonine hydrochloride in medium-moisture sugar formulations having about 2% to about 5% moisture.

Examples 29-32 in Table 5 demonstrate the use of dyclonine hydrochloride in high-moisture sugar formulations having more than about 5% moisture.

TABLE 4

| (WEIGHT PERCENT)           |        |        |        |        |
|----------------------------|--------|--------|--------|--------|
|                            | EX. 25 | EX. 26 | EX. 27 | EX. 28 |
| SUGAR                      | 53.4   | 53.2   | 53.4   | 49.7   |
| GUM BASE                   | 19.2   | 19.2   | 19.2   | 19.2   |
| CORN<br>SYRUP <sup>a</sup> | 15.0   | 15.0   | 13.0   | 12.5   |

TABLE 4-continued

| (WEIGHT PERCENT)                |        |        |        |        |
|---------------------------------|--------|--------|--------|--------|
|                                 | EX. 25 | EX. 26 | EX. 27 | EX. 28 |
| DEXTROSE                        | 10.0   | 10.0   | 10.0   | 10.0   |
| MONOHY-<br>DRATE                |        |        |        |        |
| GLYCERIN <sup>b</sup>           | 1.4    | 1.4    | 3.4    | 7.4    |
| FLAVOR                          | 0.9    | 0.9    | 0.9    | 0.9    |
| ACTIVE                          | 0.1    | 0.3    | 0.1    | 0.3    |
| DYCLONINE<br>HYDRO-<br>CHLORIDE |        |        |        |        |

<sup>a</sup>Corn syrup is evaporated to 85% solids, 15% moisture

<sup>b</sup>Glycerin and syrup may be blended and co-evaporated

TABLE 5

| (WEIGHT PERCENT)                |        |        |        |        |
|---------------------------------|--------|--------|--------|--------|
|                                 | EX. 29 | EX. 30 | EX. 31 | EX. 32 |
| SUGAR                           | 50.9   | 50.7   | 49.9   | 49.7   |
| GUM BASE                        | 24.0   | 24.0   | 24.0   | 24.0   |
| CORN<br>SYRUP                   | 24.0   | 24.0   | 24.0   | 24.6   |
| GLYCERIN                        | 0.0    | 0.0    | 1.0    | 0.4    |
| FLAVOR                          | 1.0    | 1.0    | 1.0    | 1.0    |
| ACTIVE                          | 0.1    | 0.3    | 0.1    | 0.3    |
| DYCLONINE<br>HYDRO-<br>CHLORIDE |        |        |        |        |

Examples 33-36 in Table 6 and Examples 37-44 in Tables 7 and 8 demonstrate the use of dyclonine hydrochloride in low- and high-moisture gums that are sugar-free. Low-moisture gums have less than about 2% moisture, and high-moisture gums have greater than 2% moisture.

TABLE 6

| (WEIGHT PERCENT)                |        |        |        |        |
|---------------------------------|--------|--------|--------|--------|
|                                 | EX. 33 | EX. 34 | EX. 35 | EX. 36 |
| BASE                            | 25.5   | 25.5   | 25.5   | 25.5   |
| SORBITOL                        | 50.9   | 50.7   | 48.9   | 45.7   |
| MANNITOL                        | 12.0   | 12.0   | 12.0   | 12.0   |
| GLYCERIN                        | 10.0   | 10.0   | 12.0   | 15.0   |
| FLAVOR                          | 1.5    | 1.5    | 1.5    | 1.5    |
| ACTIVE                          | 0.1    | 0.3    | 0.1    | 0.3    |
| DYCLONINE<br>HYDRO-<br>CHLORIDE |        |        |        |        |





High-intensity sweeteners (HIS) such as aspartame, acesulfame K, or the salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin, and combinations thereof may be used in any of the Examples listed in Tables 3, 4, 5, 6, 7, 8, 9 and 10. Since dyclonine hydrochloride may reduce sweetness, HIS may be used in sugar gum, and some of the alditols in sugar-free gum are less sweet than sugar so higher levels of HIS may be needed to obtain the proper level of sweetness.

High-intensity sweeteners may also be modified to control their release in those chewing gum formulations. This can be controlled by various methods of encapsulation, agglomeration, absorption, or a combination of methods to obtain either a fast or slow release of the sweetener. Sweetener combinations, some of which may be synergistic, may also be included in the gum formulations.

Example 69—A 50% shellac, 50% active dyclonine hydrochloride powder mixture is obtained by spray drying an appropriate ratio alcohol/shellac/dyclonine hydrochloride mixture at 10% solids.

Example 70—A 70% Zein, 30% active dyclonine hydrochloride powder mixture is obtained by spray drying an alcohol/Zein/dyclonine hydrochloride mixture at 10% solids.

Example 71—A 40% shellac, 60% active dyclonine hydrochloride powder mixture is obtained by fluid-bed coating dyclonine hydrochloride with an alcohol/shellac solution at 20% solids.

Example 72—A 40% Zein, 60% active dyclonine hydrochloride powder mixture is obtained by fluid-bed coating dyclonine hydrochloride with an alcohol/Zein solution of 20% solids.

Example 73—A 70% wax, 30% active dyclonine hydrochloride powder mixture is obtained by spray chilling a mixture of molten wax and dyclonine hydrochloride.

Example 74—A 70% Zein, 30% active dyclonine hydrochloride powder mixture is obtained by spray drying an aqueous mixture of dyclonine hydrochloride and Zein dispersed in an aqueous, high-pH (pH of 11.6–12.0) media at 10% solids.

Examples 69–74 would all give nearly complete encapsulation and would delay the release of dyclonine hydrochloride when used in the sugarless gum formulation. The higher levels of coating would give a longer delayed release of sweetener than the lower levels of coating.

Other polymers that are more water soluble would have less of an effect of delaying the release of the dyclonine hydrochloride if used in the coating.

Example 75—A 30% hydroxypropylmethyl cellulose (HPMC), 70% dyclonine hydrochloride powder mixture is obtained by fluid-bed coating dyclonine hydrochloride with an aqueous solution of HPMC at 10% solids.

Example 76—A 50% maltodextrin, 50% active dyclonine hydrochloride powder mixture is obtained by spray drying an aqueous mixture of dyclonine hydrochloride and maltodextrin at 20% solids.

Example 77—A 40% gum arabic, 60% active dyclonine hydrochloride powder mixture is obtained by fluid-bed coating dyclonine hydrochloride with an aqueous solution of gum arabic at 20% solids.

The coated dyclonine hydrochloride from Examples 75–77, when used in a chewing gum formula, would give a fast release of active agents.

Dyclonine hydrochloride could also be used in gum as an agglomerated active agent to give delayed sweetness

release. Agglomerated active agent can be prepared as in the following examples:

Example 78—A 15% hydroxypropylmethyl cellulose (HPMC), 85% active dyclonine hydrochloride powder mixture is prepared by agglomerating dyclonine hydrochloride and HPMC blended together, with water being added, and the resulting product being dried and ground.

Example 79—A 15% gelatin, 85% active dyclonine hydrochloride powder mixture is made by agglomerating dyclonine hydrochloride and gelatin blended together, with water being added, and the resulting product being dried and ground.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

Keeping this in mind, if a coating of about 25% of the total product is added to a pellet core as sugar or polyols, the gum base in the pellet core should also be increased by 25%. Likewise, if a 33% coating is applied, the base levels should also be increased by 33%. As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type gum center formulations are shown in Table 11. Gum center formulas may or may not contain dyclonine hydrochloride.

TABLE 11

(WEIGHT PERCENT)

|                         | EX. 80 | EX. 81 | EX. 82 | EX. 83 | EX. 84 | EX. 85 |
|-------------------------|--------|--------|--------|--------|--------|--------|
| SUGAR                   | 52.0   | 48.7   | 47.55  | 44.0   | 40.7   | 38.55  |
| GUM BASE                | 26.0   | 30.0   | 35.00  | 26.0   | 30.0   | 35.00  |
| CORN SYRUP              | 20.0   | 19.0   | 15.00  | 18.0   | 17.0   | 14.00  |
| GLYCERIN                | 1.0    | 1.0    | 1.00   | 1.0    | 1.0    | 1.00   |
| PEPPERMINT FLAVOR       | 1.0    | 1.0    | 1.00   | 1.0    | 1.0    | 1.00   |
| DEXTROSE MONO-HYDRATE   | —      | —      | —      | 10.0   | 10.0   | 10.00  |
| DYCLONINE HYDROCHLORIDE | —      | 0.3    | 0.45   | —      | 0.3    | 0.45   |

Formulations with or without active dyclonine hydrochloride can also be made similar to those found in Tables 3–8 for low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars and polyols may be used in the gum center as found in Tables 9–10. Dyclonine hydrochloride may be added to a gum center only, or to a gum coating with none in the center, or to both center and coating. Coated gum pieces are about 1.5 grams, so to obtain 3 mg of dyclonine hydrochloride total piece must contain 0.2%.

Dyclonine hydrochloride can then be used in the coating formula on the various pellet gum formulations. The fol-

lowing Table 12 shows some sugar and dextrose type formulas:

TABLE 12

| (DRY WEIGHT PERCENT)     |        |        |                  |        |        |                  |
|--------------------------|--------|--------|------------------|--------|--------|------------------|
|                          | EX. 88 | EX. 87 | EX. 88           | EX. 89 | EX. 90 | EX. 91           |
| SUGAR                    | 97.1   | 95.2   | 93.5             | 96.9   | 94.9   | 93.0             |
| GUM ARABIC               | 2.0    | 3.0    | 4.0              | 2.0    | 3.0    | 4.0              |
| TITANIUM DIOXIDE         | 0.5    | 1.0    | 1.0              | —      | —      | —                |
| CALCIUM CARBONATE        | —      | —      | —                | 0.5    | 1.0    | 2.0              |
| FLAVOR                   | 0.3    | 0.5    | 0.8              | 0.5    | 0.8    | 0.3              |
| WAX                      | 0.1    | 0.1    | 0.1              | 0.1    | 0.1    | 0.1              |
| DYCLONINE HYDRO-CHLORIDE | —      | 0.2    | 0.6 <sup>a</sup> | —      | 0.2    | 0.6 <sup>a</sup> |

|                          | EX. 92 | EX. 93 | EX. 94 | EX. 95           |
|--------------------------|--------|--------|--------|------------------|
| DEXTROSE MONO-HYDRATE    | 97.6   | 95.2   | 97.0   | 93.9             |
| GUM ARABIC               | 1.5    | 3.0    | 1.5    | 3.0              |
| TITANIUM DIOXIDE         | 0.5    | 1.0    | —      | —                |
| CALCIUM CARBONATE        | —      | —      | 1.0    | 2.0              |
| FLAVOR                   | 0.3    | 0.5    | 0.2    | 0.4              |
| WAX                      | 0.1    | 0.1    | 0.1    | 0.1              |
| DYCLONINE HYDRO-CHLORIDE | —      | 0.2    | 0.2    | 0.6 <sup>a</sup> |

|                       | EX. 96 | EX. 97 | EX. 98 | EX. 99 | EX. 100 | EX. 101 |
|-----------------------|--------|--------|--------|--------|---------|---------|
| SUGAR                 | 77.5   | 81.2   | —      | —      | 86.9    | —       |
| DEXTROSE MONO-HYDRATE | —      | —      | 77.5   | 86.1   | —       | 86.5    |
| POWDER SUGAR          | 20.0   | 15.0   | —      | —      | —       | —       |
| POWDER DEXTROSE       | —      | —      | 20.0   | 10.0   | —       | —       |
| GUM ARABIC            | 2.0    | 3.0    | 2.0    | 3.0    | 8.0     | 8.0     |
| GUM ARABIC SOLUTION   | —      | —      | —      | —      | 4.0     | 4.0     |
| FLAVOR                | 0.4    | 0.5    | 0.4    | 0.6    | 0.4     | 0.8     |
| WAX                   | 0.1    | 0.1    | 0.1    | 0.1    | 0.1     | 0.1     |

TABLE 12-continued

|                            | (DRY WEIGHT PERCENT) |     |   |     |                  |                  |
|----------------------------|----------------------|-----|---|-----|------------------|------------------|
| 5 DYCLONINE HYDRO-CHLORIDE | —                    | 0.2 | — | 0.2 | 0.6 <sup>a</sup> | 0.6 <sup>a</sup> |

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product.

10 The above process gives a hard shell coating. Often a dry charge of powdered sugar or dextrose monohydrate may be used. This gives a somewhat softer coating. A dry charge may be used to build up a coating, but then finished with a straight syrup to obtain a hard shell. Table 12 gives these types of formulas.

15 In Examples 96-99, gum arabic is blended in the sugar syrup. In Examples 100 and 101, gum arabic powder is dry charged after a gum arabic solution is applied in the first stages of coating, then this is followed by a hard shell coating of sugar solution or dextrose solution.

20 The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide or calcium carbonate in this syrup. Some of the dextrose may be added as a dry charge which may also contain the active agent. Dyclonine hydrochloride may be dissolved in water, not mixed with hot syrup, but added between coatings, or it may be added to the hot syrup and used in the early stages of coating or used throughout the coating process. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. Dyclonine hydrochloride may be dissolved in flavor and added to the coating. After the final coats are applied and dried, wax is applied to give a smooth polish.

30 Dyclonine hydrochloride may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations with and without dyclonine hydrochloride similar to those found in Tables 6, 7 or 8 for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30-46% with the other ingredients proportionally reduced. Some typical gum formulas are in Table 13.

TABLE 13

|   | (WEIGHT PERCENT) |         |                       |         |         |                   |                       |
|---|------------------|---------|-----------------------|---------|---------|-------------------|-----------------------|
|   | EX. 102          | EX. 103 | EX. 104 <sup>b)</sup> | EX. 105 | EX. 106 | EX. 107           | EX. 108 <sup>c)</sup> |
| GUM BASE                                      | 35.0             | 35.0    | 30.0                  | 30.0    | 30.0    | 40.0              | 50.0                  |
| CALCIUM CARBONATE                             | —                | —       | 5.0                   | 10.0    | 15.0    | —                 | —                     |
| SORBITOL                                      | 43.3             | 45.0    | 45.9                  | 40.3    | 44.5    | 41.4              | 26.1                  |
| MANNITOL                                      | 10.0             | 10.0    | 5.0                   | 10.0    | —       | 8.0               | 10.0                  |
| GLYCERIN                                      | —                | 8.0     | 2.0                   | —       | 8.0     | 2.0               | 2.0                   |
| SORBITOL LIQUID                               | 10.0             | —       | 10.0                  | 8.0     | —       | 6.0 <sup>b)</sup> | 10.0 <sup>b)</sup>    |
| FLAVOR  | 1.5              | 1.5     | 1.5                   | 1.5     | 2.0     | 2.0               | 1.3                   |
| HIGH INTENSITY SWEETENER                      | 0.2              | 0.2     | 0.2                   | 0.2     | 0.2     | 0.3               | 0.2                   |
| ACTIVE DYCLONINE HYDRO-CHLORIDE <sup>b)</sup> | —                | 0.3     | 0.4                   | —       | 0.3     | 0.3               | 0.4                   |

<sup>b)</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid

<sup>b)</sup>This material may be dissolved in water, glycerin, sorbitol liquid, or HSH.

<sup>c)</sup>These formulas require 50% of the product to be a coating with no active agent, to give a final product with 0.2% active agent.

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, xylitol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels similar to those shown in Table 10. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Dyclonine hydrochloride may be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. The following table gives formulas for a xylitol coating:

TABLE 14

| (DRY WEIGHT PERCENT)    |         |         |         |         |         |         |
|-------------------------|---------|---------|---------|---------|---------|---------|
|                         | EX. 109 | EX. 110 | EX. 111 | EX. 112 | EX. 113 | EX. 114 |
| XYLITOL                 | 94.8    | 92.2    | 90.1    | 90.1    | 89.7    | 88.2    |
| GUM ARABIC              | 4.0     | 6.0     | 7.0     | 8.5     | 8.5     | 10.0    |
| FLAVOR                  | 0.5     | 0.5     | 0.7     | 0.7     | 0.9     | 0.5     |
| TITANIUM DIOXIDE        | 0.5     | 0.9     | —       | 0.5     | 0.5**   | 0.5**   |
| TALC                    | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX                     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| COLOR*                  | —       | —       | 1.4     | —       | —       | —       |
| DYCLONINE HYDROCHLORIDE | —       | 0.2     | 0.6*    | —       | 0.2     | 0.6*    |

\*Lake color dispersed in xylitol solution

\*\*Calcium carbonate used in place of titanium dioxide

\*All of the active agent is in the gum coating, which comprises 33% of the gum product.

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. Dyclonine hydrochloride may be dissolved in water and added between coating applications or mixed with the hot syrup and used in the early stages of coating or used throughout the coating process. After pellets have been coated and dried, talc and wax are added to give a polish.

For examples 115-120, erythritol may be substituted for xylitol in Table 14. In some cases more gum arabic may be needed to give good binding.

For coating formulas based on sorbitol, maltitol, lactitol, and hydrogenated isomaltulose, gum arabic can be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols are more difficult to coat using only a straight syrup, but with proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The following formulations may be used.

TABLE 15

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 121 | EX. 122 | EX. 123 | EX. 124 | EX. 125 | EX. 126 |
| MALTTTOL             | 98.8    | 94.7    | 91.5    | 86.8    | 75.9    | 68.9    |
| MALTTTOL             | —       | —       | —       | 10.0    | 20.0    | 25.0    |

TABLE 15-continued

| (DRY WEIGHT PERCENT)    |         |         |         |         |         |         |
|-------------------------|---------|---------|---------|---------|---------|---------|
|                         | EX. 121 | EX. 122 | EX. 123 | EX. 124 | EX. 125 | EX. 126 |
| POWDER                  |         |         |         |         |         |         |
| GUM ARABIC              | 2.0     | 4.0     | 6.0     | 2.0     | 3.0     | 4.0     |
| FLAVOR                  | 0.5     | 0.4     | 0.7     | 0.5     | 0.3     | 0.7     |
| TITANIUM DIOXIDE        | 0.5     | 0.5     | 1.0     | 0.5     | 0.4     | 0.6     |
| TALC                    | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX                     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| DYCLONINE HYDROCHLORIDE | —       | 0.2     | 0.6*    | —       | 0.2     | 0.6*    |

\*All of the active agent is in the coating, which comprises 33% of the product.

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener are blended into a syrup and applied to pellets. Dyclonine hydrochloride may be applied in a similar manner as in the previous xylitol coating or may be preblended with the dry charge material. After all coating is applied and dried, talc and wax are added to give a polish.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 15 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, calcium carbonate, magnesium carbonate, starches, gums like dyclonine hydrochloride, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge, along with the active medicament.

Some polyols such as sorbitol, maltitol, lactitol, erythritol, or hydrogenated isomaltulose are not sufficiently sweet compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

The formulas listed in Table 16 comprise various sugar-type formulas in which chlorpheniramine maleate can be added to gum after it is dissolved in water or mixed with various aqueous solvents. Chlorpheniramine maleate is an active medicament used as an antihistamine. These formulas give a 3 gram stick with 4 mg of chlorpheniramine maleate.

TABLE 16

|                     | (WEIGHT PERCENT) |         |         |         |         |         |         |         |
|---------------------|------------------|---------|---------|---------|---------|---------|---------|---------|
|                     | EX. 127          | EX. 128 | EX. 129 | EX. 130 | EX. 131 | EX. 132 | EX. 133 | EX. 134 |
| SUGAR               | 62.47            | 64.3    | 63.0    | 64.4    | 64.4    | 62.7    | 61.6    | 47.0    |
| BASE                | 19.2             | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    |
| CORN SYRUP          | 15.9             | 12.9    | 12.9    | 12.9    | 12.9    | 15.9    | 0.0     | 2.9     |
| PEPPER-MINT FLAVOR  | 0.9              | 0.9     | 0.9     | 0.9     | 0.0     | 0.0     | 0.9     | 0.9     |
| GLYCERIN            | 1.4              | 1.4     | 1.4     | 0.0     | 2.2     | 0.9     | 1.4     | 0.0     |
| LIQUID/ACTIVE BLEND | 0.13             | 1.3     | 2.6     | 2.6     | 1.3     | 1.3     | 16.9    | 30.0    |

## Example 127

Chlorpheniramine maleate powder can be added directly<sup>20</sup> to the gum.

## Example 128

A 1 gram quantity of chlorpheniramine maleate can be<sup>25</sup> dissolved in 9 grams of water giving a 10% solution and added to gum.

## Example 129

A 1 gram quantity of chlorpheniramine maleate can be<sup>30</sup> dissolved in 9 grams of water and mixed with 10 grams of glycerin and added to the gum.

## Example 130

A 1 gram quantity of chlorpheniramine maleate is mixed<sup>35</sup> with 19 grams of glycerin giving a 5% solution and added to gum.

## Example 131

A 1 gram quantity of chlorpheniramine maleate is mixed<sup>40</sup> with 9 grams of peppermint flavor giving a 10% solution and added to gum.

## Example 133

A 1.3 gram quantity of chlorpheniramine maleate is dissolved in 168 grams of corn syrup and added to chewing gum.

## Example 134

To a 200 gram quantity of corn syrup is added 100 grams of glycerin.

To this mixture is added 1.3 gram of chlorpheniramine maleate and blended. This mixture is then added to gum.

In the next examples of sugar formulations, chlorpheniramine maleate can be dissolved in water and emulsifiers<sup>35</sup> can be added to the aqueous solution. Example solutions can be prepared by dissolving 13 grams of chlorpheniramine maleate in 72 grams of water and adding 15 grams of emulsifiers of various hydrophilic-lipophilic balance (HLB) values to the solution. The mixtures can then be used in the following formulas. Example 135 uses a mixture of chlorpheniramine maleate and water with no emulsifier. The HLB value of the emulsifiers used in Examples 136-140 are listed in Table 17.

TABLE 17

|                          | (WEIGHT PERCENT) |         |         |         |         |          |
|--------------------------|------------------|---------|---------|---------|---------|----------|
|                          | EX. 135          | EX. 136 | EX. 137 | EX. 138 | EX. 139 | EX. 140  |
| SUGAR                    | 54.7             | 54.7    | 54.7    | 54.7    | 54.7    | 54.7     |
| BASE                     | 19.2             | 19.2    | 19.2    | 19.2    | 19.2    | 19.2     |
| CORN SYRUP               | 12.9             | 12.9    | 12.9    | 12.9    | 12.9    | 12.9     |
| GLYCERIN                 | 1.4              | 1.4     | 1.4     | 1.4     | 1.4     | 1.4      |
| DEXTROSE MONOHYDRATE     | 9.9              | 9.9     | 9.9     | 9.9     | 9.9     | 9.9      |
| PEPP. FLAVOR             | 0.9              | 0.9     | 0.9     | 0.9     | 0.9     | 0.9      |
| ACTIVE AGENT             | 1.0              | 1.0     | 1.0     | 1.0     | 1.0     | 1.0      |
| EMULSIFIER/WATER MIXTURE | None             | HLB - 2 | HLB - 4 | HLB - 6 | HLB - 9 | HLB - 12 |

## Example 132

A 1 gram quantity of chlorpheniramine maleate is dis-<sup>65</sup> solved in 9 grams of ethanol, which is then mixed with 90 grams of peppermint flavor and added to gum.

## Examples 141-146

The same as the formulations made in Examples 135-140, respectively, except that the flavor can be mixed

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together with the aqueous active agent solution and emulsified before adding the mixture to the gum batch.

The following Tables 18 through 25 are examples of gum formulations that demonstrate formula variations in which chlorpheniramine maleate may be used. The active agent may be added with or without encapsulation, or may be treated for fast release.

Examples 147-150 in Table 18 demonstrate the use of chlorpheniramine maleate in low-moisture sugar formulations showing less than 2% theoretical moisture:

TABLE 18

| (WEIGHT PERCENT)         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|
|                          | EX. 147 | EX. 148 | EX. 149 | EX. 150 |
| SUGAR                    | 58.77   | 58.51   | 58.77   | 54.51   |
| GUM BASE                 | 19.2    | 19.2    | 19.2    | 19.2    |
| CORN <sup>a</sup>        | 6.0     | 6.0     | —       | —       |
| SYRUP                    | —       | —       | —       | —       |
| DEXTROSE                 | 10.0    | 10.0    | 10.0    | 10.0    |
| MONOHYDRATE              | —       | —       | —       | —       |
| LACTOSE                  | 0.0     | 0.0     | 0.0     | 5.0     |
| GLYCERIN <sup>b</sup>    | 5.0     | 5.0     | 11.0    | 10.0    |
| FLAVOR                   | 0.9     | 0.9     | 0.9     | 0.9     |
| ACTIVE                   | 0.13    | 0.39    | 0.13    | 0.39    |
| CHLORPHENIRAMINE MALEATE | —       | —       | —       | —       |

<sup>a</sup>Corn syrup is evaporated to 85% solids, 15% moisture

<sup>b</sup>Glycerin and syrup may be blended and co-evaporated

Examples 151-154 in Table 19 demonstrate the use of chlorpheniramine maleate in medium-moisture sugar formulations having about 2% to about 5% moisture.

Examples 155-158 in Table 20 demonstrate the use of chlorpheniramine maleate in high-moisture sugar formulations having more than about 5% moisture.

TABLE 19

| (WEIGHT PERCENT)         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|
|                          | EX. 151 | EX. 152 | EX. 153 | EX. 154 |
| SUGAR                    | 53.37   | 53.11   | 53.37   | 49.61   |
| GUM BASE                 | 19.2    | 19.2    | 19.2    | 19.2    |
| CORN                     | 15.0    | 15.0    | 13.0    | 12.5    |
| SYRUP <sup>a</sup>       | —       | —       | —       | —       |
| DEXTROSE                 | 10.0    | 10.0    | 10.0    | 10.0    |
| MONOHYDRATE              | —       | —       | —       | —       |
| LACTOSE                  | —       | —       | —       | —       |
| GLYCERIN <sup>b</sup>    | 1.4     | 1.4     | 3.4     | 7.4     |
| FLAVOR                   | 0.9     | 0.9     | 0.9     | 0.9     |
| ACTIVE                   | 0.13    | 0.39    | 0.13    | 0.39    |
| CHLORPHENIRAMINE MALEATE | —       | —       | —       | —       |

<sup>a</sup>Corn syrup is evaporated to 85% solids, 15% moisture

<sup>b</sup>Glycerin and syrup may be blended and co-evaporated

TABLE 20

| (WEIGHT PERCENT) |         |         |         |         |
|------------------|---------|---------|---------|---------|
|                  | EX. 155 | EX. 156 | EX. 157 | EX. 158 |
| SUGAR            | 50.87   | 50.51   | 49.87   | 49.61   |
| GUM BASE         | 24.0    | 24.0    | 24.0    | 24.0    |
| CORN             | 24.0    | 24.0    | 24.0    | 24.6    |
| SYRUP            | —       | —       | —       | —       |

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TABLE 20-continued

| (WEIGHT PERCENT)         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|
|                          | EX. 155 | EX. 156 | EX. 157 | EX. 158 |
| GLYCERIN                 | 0.0     | 0.0     | 1.0     | 0.4     |
| FLAVOR                   | 1.0     | 1.0     | 1.0     | 1.0     |
| ACTIVE                   | 0.13    | 0.39    | 0.13    | 0.39    |
| CHLORPHENIRAMINE MALEATE | —       | —       | —       | —       |

Examples 159-162 in Table 21 and Examples 163-170 in Tables 22 and 23 demonstrate the use of chlorpheniramine maleate in low- and high-moisture gums that are sugar-free. Low-moisture gums have less than about 2% moisture, and high-moisture gums have greater than 2% moisture.

TABLE 21

| (WEIGHT PERCENT)         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|
|                          | EX. 159 | EX. 160 | EX. 161 | EX. 162 |
| BASE                     | 25.5    | 25.5    | 25.5    | 25.5    |
| SORBITOL                 | 50.87   | 50.61   | 48.87   | 45.61   |
| MANNITOL                 | 12.0    | 12.0    | 12.0    | 12.0    |
| GLYCERIN                 | 10.0    | 10.0    | 12.0    | 15.0    |
| FLAVOR                   | 1.5     | 1.5     | 1.5     | 1.5     |
| ACTIVE                   | 0.13    | 0.39    | 0.13    | 0.39    |
| CHLORPHENIRAMINE MALEATE | —       | —       | —       | —       |

TABLE 22

| (WEIGHT PERCENT)         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|
|                          | EX. 163 | EX. 164 | EX. 165 | EX. 166 |
| BASE                     | 25.5    | 25.5    | 25.5    | 25.5    |
| SORBITOL                 | 50.87   | 50.61   | 40.87   | 40.61   |
| LIQUID                   | 10.0    | 10.0    | 20.0    | 20.0    |
| SORBITOL*                | —       | —       | —       | —       |
| MANNITOL                 | 10.0    | 10.0    | 10.0    | 10.0    |
| GLYCERIN                 | 2.0     | 2.0     | 2.0     | 2.0     |
| FLAVOR                   | 1.5     | 1.5     | 1.5     | 1.5     |
| ACTIVE                   | 0.13    | 0.39    | 0.13    | 0.39    |
| CHLORPHENIRAMINE MALEATE | —       | —       | —       | —       |

\*Sorbitol liquid contains 70% sorbitol, 30% water

TABLE 23

| (WEIGHT PERCENT)         |         |         |         |         |
|--------------------------|---------|---------|---------|---------|
|                          | EX. 167 | EX. 168 | EX. 169 | EX. 170 |
| BASE                     | 25.5    | 25.5    | 25.5    | 25.5    |
| SORBITOL                 | 50.87   | 48.61   | 44.87   | 42.61   |
| HSR SYRUP*               | 10.0    | 10.0    | 10.0    | 10.0    |
| MANNITOL                 | 8.0     | 8.0     | 8.0     | 8.0     |
| GLYCERIN**               | 4.0     | 6.0     | 10.0    | 12.0    |
| FLAVOR                   | 1.5     | 1.5     | 1.5     | 1.5     |
| ACTIVE                   | 0.13    | 0.39    | 0.13    | 0.39    |
| CHLORPHENIRAMINE MALEATE | —       | —       | —       | —       |

\*Hydrogenated starch hydrolyzate syrup

\*\*Glycerin and HSR syrup may be blended or co-evaporated

Table 24 shows sugar chewing formulations that can be made with various types of sugars.

TABLE 24

| (WEIGHT PERCENT)                 |         |         |         |         |         |         |
|----------------------------------|---------|---------|---------|---------|---------|---------|
|                                  | EX. 171 | EX. 172 | EX. 173 | EX. 174 | EX. 175 | EX. 176 |
| GUM BASE                         | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    |
| SUCROSE                          | 49.37   | 48.11   | 44.37   | 39.11   | 34.37   | 42.11   |
| GLYCERIN                         | 1.4     | 2.4     | 1.4     | 6.4     | 1.4     | 3.4     |
| CORN SYRUP                       | 14.0    | 14.0    | 14.0    | 14.0    | 14.0    | 14.0    |
| DEXTROSE                         | 5.0     | 5.0     | —       | —       | 10.0    | 5.0     |
| LACTOSE                          | 5.0     | 5.0     | 10.0    | 10.0    | —       | —       |
| FRUCTOSE                         | 5.0     | 5.0     | 10.0    | 10.0    | 10.0    | 5.0     |
| INVERT SUGAR                     | —       | —       | —       | —       | 10.0    | 10.0    |
| MALTOSE                          | —       | —       | —       | —       | —       | —       |
| CORN SYRUP SOLIDS                | —       | —       | —       | —       | —       | —       |
| PEPPERMINT FLAVOR                | 0.9     | 0.9     | 0.9     | 0.9     | 0.9     | 0.9     |
| ACTIVE CHLORPHEN-IRAMINE MALEATE | 0.13    | 0.39    | 0.13    | 0.39    | 0.13    | 0.39    |

|                                  | EX. 177 | EX. 178 | EX. 179 | EX. 180 | EX. 181 | EX. 182 |
|----------------------------------|---------|---------|---------|---------|---------|---------|
| GUM BASE                         | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    |
| SUCROSE                          | 34.37   | 43.11   | 34.37   | 43.11   | 42.37   | 45.11   |
| GLYCERIN                         | 1.4     | 2.4     | 1.4     | 2.4     | 1.4     | 3.4     |
| CORN SYRUP                       | 14.0    | 14.0    | 14.0    | 14.0    | 11.0    | 11.0    |
| DEXTROSE                         | 10.0    | 5.0     | 10.0    | 5.0     | 10.0    | 5.0     |
| LACTOSE                          | —       | —       | —       | —       | —       | —       |
| FRUCTOSE                         | 10.0    | 5.0     | 10.0    | 5.0     | 5.0     | 5.0     |
| INVERT SUGAR                     | 10.0    | 10.0    | —       | —       | 5.0     | 5.0     |
| MALTOSE                          | —       | —       | 10.0    | 10.0    | —       | —       |
| CORN SYRUP SOLIDS                | —       | —       | —       | —       | 5.0     | 5.0     |
| PEPPERMINT FLAVOR                | 0.9     | 0.9     | 0.9     | 0.9     | 0.9     | 0.9     |
| ACTIVE CHLORPHEN-IRAMINE MALEATE | 0.13    | 0.39    | 0.13    | 0.39    | 0.13    | 0.39    |

Table 25 shows chewing gum formulations that are free of sugar. These formulations can use a wide variety of other non-sugar alditols.

TABLE 25

| (WEIGHT PERCENT)                 |         |         |         |         |         |         |
|----------------------------------|---------|---------|---------|---------|---------|---------|
|                                  | EX. 183 | EX. 184 | EX. 185 | EX. 186 | EX. 187 | EX. 188 |
| GUM BASE                         | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    |
| GLYCERIN                         | 8.0     | 8.0     | 8.0     | 8.0     | 8.0     | 2.0     |
| SORBITOL                         | 47.87   | 37.611  | 37.87   | 32.61   | 31.87   | 29.61   |
| MANNITOL                         | —       | 10.0    | 10.0    | 10.0    | 10.0    | 6.0     |
| SORBITOL LIQUID                  | 17.0    | 17.0    | —       | —       | —       | —       |
| LYCASIN                          | —       | —       | 17.0    | 12.0    | 8.0     | 20.0    |
| MALTTTOL                         | —       | —       | —       | 10.0    | —       | —       |
| XYLITOL                          | —       | —       | —       | —       | 15.0    | 15.0    |
| LACITTOL                         | —       | —       | —       | —       | —       | —       |
| PALATINT                         | —       | —       | —       | —       | —       | —       |
| FLAVOR                           | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     |
| ACTIVE CHLORPHEN-IRAMINE MALEATE | 0.13    | 0.39    | 0.13    | 0.39    | 0.13    | 0.39    |

|                 | EX. 189 | EX. 190 | EX. 191 | EX. 192 | EX. 193 | EX. 194 |
|-----------------|---------|---------|---------|---------|---------|---------|
| GUM BASE        | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    |
| GLYCERIN        | 8.0     | 8.0     | 8.0     | 2.0     | 8.0     | 2.0     |
| SORBITOL        | 41.87   | 36.61   | 31.87   | 40.61   | 29.87   | 29.61   |
| MANNITOL        | 8.0     | 8.0     | 8.0     | —       | —       | —       |
| SORBITOL LIQUID | 5.0     | —       | —       | —       | —       | —       |
| LYCASIN         | —       | 5.0     | 5.0     | 5.0     | 10.0    | 20.0    |
| MALTTTOL        | —       | 5.0     | —       | —       | —       | —       |



TABLE 25-continued

| (WEIGHT PERCENT)                |      |      |      |      |      |      |
|---------------------------------|------|------|------|------|------|------|
| XYLITOL                         | —    | —    | —    | 15.0 | 15.0 | 11.0 |
| LACTITOL                        | 10.0 | 10.0 | 10.0 | —    | —    | —    |
| PALATINIT                       | —    | —    | 10.0 | 10.0 | 10.0 | 10.0 |
| FLAVOR                          | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  | 1.5  |
| ACTIVE CHLORPHENIRAMINE MALEATE | 0.13 | 0.39 | 0.13 | 0.39 | 0.13 | 0.39 |

High-intensity sweeteners (HIS) such as aspartame, acesulfame K, or the salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin, and combinations thereof may be used in any of the Examples listed in Tables 18–25. Since chlorpheniramine maleate may reduce sweetness, HIS may be used in sugar gum, and some of the alditols in sugar-free gum are less sweet than sugar so higher levels of HIS may be needed to obtain the proper level of sweetness.

High-intensity sweeteners (HIS) may also be modified to control their release in those chewing gum formulations. This can be controlled by various methods of encapsulation, agglomeration, absorption, or a combination of methods to obtain either a fast or slow release of the sweetener. Sweetener combinations, some of which may be synergistic, may also be included in the gum formulations.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type gum center formulations are shown in Table 26. Gum center formulas may or may not contain chlorpheniramine maleate.

TABLE 26

| (WEIGHT PERCENT)                |                 |         |         |                 |         |         |
|---------------------------------|-----------------|---------|---------|-----------------|---------|---------|
|                                 | EX. 195         | EX. 196 | EX. 197 | EX. 198         | EX. 199 | EX. 200 |
| SUGAR                           | 52.0            | 48.73   | 47.59   | 44.0            | 40.73   | 38.59   |
| GUM BASE                        | 26.0            | 30.0    | 35.00   | 26.0            | 30.0    | 35.00   |
| CORN SYRUP                      | 20.0            | 19.0    | 15.00   | 18.0            | 17.0    | 14.00   |
| GLYCERIN                        | 1.0             | 1.0     | 1.00    | 1.0             | 1.0     | 1.00    |
| PEPPERMINT FLAVOR               | 1.0             | 1.0     | 1.00    | 1.0             | 1.0     | 1.00    |
| DEXTROSE MONOHYDRATE            | —               | —       | —       | 10.0            | 10.0    | 10.00   |
| ACTIVE CHLORPHENIRAMINE MALEATE | — <sup>a)</sup> | 0.27    | 0.41    | — <sup>a)</sup> | 0.27    | 0.41    |

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

Formulations with or without active chlorpheniramine maleate can also be made similar to those found in Tables 18–23 for low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars or polyols may be used in the gum center as found in Tables 24 and 25. Chlorpheniramine maleate may be added to a gum center only, or to a gum coating with none in the center, or to both center and coating. Coated gum pieces are about 1.5 grams, so to obtain 4 mg of chlorpheniramine maleate total piece must contain 0.27%.

Chlorpheniramine maleate can be used in the coating formula on the various pellet gum formulations. The following Table 27 shows some sugar and dextrose type formulas:

TABLE 27

| (DRY WEIGHT PERCENT)     |         |         |                    |         |         |                    |
|--------------------------|---------|---------|--------------------|---------|---------|--------------------|
|                          | EX. 201 | EX. 202 | EX. 203            | EX. 204 | EX. 205 | EX. 206            |
| SUGAR                    | 97.1    | 95.13   | 93.29              | 96.9    | 94.83   | 92.79              |
| GUM ARABIC               | 2.0     | 3.0     | 4.0                | 2.0     | 3.0     | 4.0                |
| TITANIUM DIOXIDE         | 0.5     | 1.0     | 1.0                | —       | —       | —                  |
| CALCIUM CARBONATE        | —       | —       | —                  | 0.5     | 1.0     | 2.0                |
| FLAVOR                   | 0.3     | 0.5     | 0.8                | 0.5     | 0.8     | 0.3                |
| WAX                      | 0.1     | 0.1     | 0.1                | 0.1     | 0.1     | 0.1                |
| CHLORPHENIRAMINE MALEATE | —       | 0.27    | 0.81 <sup>a)</sup> | —       | 0.27    | 0.81 <sup>a)</sup> |
|                          | EX. 207 | EX. 208 | EX. 209            | EX. 210 |         |                    |
| DEXTROSE MONOHYDRATE     | 97.6    | 95.13   | 96.93              | 93.69   |         |                    |
| GUM ARABIC               | 1.5     | 3.0     | 1.5                | 3.0     |         |                    |

TABLE 27-continued

| (DRY WEIGHT PERCENT)     |     |      |      |                    |
|--------------------------|-----|------|------|--------------------|
| TITANIUM DIOXIDE         | 0.5 | 1.0  | —    | —                  |
| CALCIUM CARBONATE        | —   | —    | 1.0  | 2.0                |
| FLAVOR                   | 0.3 | 0.5  | 0.2  | 0.4                |
| WAX                      | 0.1 | 0.1  | 0.1  | 0.1                |
| CHLORPHENIRAMINE MALEATE | —   | 0.27 | 0.27 | 0.81 <sup>a)</sup> |

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide or calcium carbonate in this syrup. Some of the dextrose may be added as a dry charge, which may also contain the active. Chlorpheniramine maleate may be dissolved in water, not mixed with hot syrup, but applied between coatings, or it may be added to the hot syrup and used in the early stages of coating or used throughout the coating process. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. Chlorpheniramine maleate may be dissolved in flavor and added to the coating. After the final coats are applied and dried, wax is applied to give a smooth polish.

Chlorpheniramine maleate may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations with and without chlorpheniramine maleate similar to those found in Tables 21-25 for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30-46% with the other ingredients proportionally reduced. Some typical gum formulas are in Table 28.

TABLE 28

| (WEIGHT PERCENT)                              |                 |         |         |                 |         |                   |                    |
|---|-----------------|---------|---------|-----------------|---------|-------------------|--------------------|
|   | EX. 211         | EX. 212 | EX. 213 | EX. 214         | EX. 215 | EX. 216           | EX. 217            |
| GUM BASE                                      | 35.0            | 35.0    | 30.0    | 30.0            | 30.0    | 40.0              | 50.0               |
| CALCIUM CARBONATE                             | —               | —       | 5.0     | 10.0            | 15.0    | —                 | —                  |
| SORBITOL                                      | 43.3            | 45.03   | 45.89   | 40.3            | 44.53   | 41.29             | 25.96              |
| MANNITOL                                      | 10.0            | 10.0    | 5.0     | 10.0            | —       | 8.0               | 10.0               |
| GLYCERIN                                      | —               | 8.0     | 2.0     | —               | 8.0     | 2.0               | 2.0                |
| SORBITOL LIQUID                               | 10.0            | —       | 10.0    | 8.0             | —       | 6.0 <sup>b)</sup> | 10.0 <sup>b)</sup> |
| FLAVOR  | 1.5             | 1.5     | 1.5     | 1.5             | 2.0     | 2.0               | 1.3                |
| HIGH INTENSITY SWEETENER                      | 0.2             | 0.2     | 0.2     | 0.2             | 0.2     | 0.3               | 0.2                |
| ACTIVE CHLORPHENIRAMINE MALEATE <sup>c)</sup> | — <sup>c)</sup> | 0.27    | 0.41    | — <sup>c)</sup> | 0.27    | 0.41              | 0.54 <sup>d)</sup> |

<sup>b)</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid

<sup>c)</sup>This material may be dissolved in water, glycerin, sorbitol liquid, or HSH.

<sup>d)</sup>All of the active agent is in the coating, which comprises 33% of the product.

<sup>e)</sup>This example required 50% of the product to be a coating with no active agent in the coating, to give a gum product with 0.27% active agent.

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrr-

rhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, xylitol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels similar to those shown in Table 25. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Chlorpheniramine maleate may be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. The following table gives formulas for a xylitol coating:

TABLE 29

| (DRY WEIGHT PERCENT)     |         |         |                    |         |         |                    |
|--------------------------|---------|---------|--------------------|---------|---------|--------------------|
|                          | EX. 218 | EX. 219 | EX. 220            | EX. 221 | EX. 222 | EX. 223            |
| XYLITOL                  | 94.8    | 92.13   | 89.89              | 90.1    | 89.63   | 87.99              |
| GUM ARABIC               | 4.0     | 6.0     | 7.0                | 8.5     | 8.5     | 10.0               |
| FLAVOR                   | 0.5     | 0.5     | 0.7                | 0.7     | 0.9     | 0.5                |
| TITANIUM DIOXIDE         | 0.5     | 0.9     | —                  | 0.5     | 0.5**   | 0.5**              |
| TALC                     | 0.1     | 0.1     | 0.1                | 0.1     | 0.1     | 0.1                |
| WAX                      | 0.1     | 0.1     | 0.1                | 0.1     | 0.1     | 0.1                |
| COLOR*                   | —       | —       | 1.4                | —       | —       | —                  |
| CHLORPHENIRAMINE MALEATE | —       | 0.27    | 0.81 <sup>b)</sup> | —       | 0.27    | 0.81 <sup>b)</sup> |

\*Lake color dispersed in xylitol solution

\*\*Calcium carbonate used in place of titanium dioxide

<sup>b)</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. Chlorpheniramine maleate may be dissolved in water or flavor and added between coating applications or mixed with

the hot syrup and used in the early stages of coating or used throughout the coating process. After pellets have been coated and dried, talc and wax are added to give a polish.

For coating formulas based on sorbitol, maltitol, lactitol, erythritol, and hydrogenated isomaltulose, gum arabic can

be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols are more difficult to coat using only a straight syrup, but with proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The following formulations may be used.

TABLE 30

| (DRY WEIGHT PERCENT)      |         |         |                    |         |         |                    |
|---------------------------|---------|---------|--------------------|---------|---------|--------------------|
|                           | EX. 224 | EX. 225 | EX. 226            | EX. 227 | EX. 228 | EX. 229            |
| MALTTITOL                 | 96.8    | 94.63   | 91.29              | 86.8    | 75.83   | 68.69              |
| MALTTITOL POWDER          | —       | —       | —                  | 10.0    | 20.0    | 25.0               |
| GUM ARABIC                | 2.0     | 4.0     | 6.0                | 2.0     | 3.0     | 4.0                |
| FLAVOR                    | 0.5     | 0.4     | 0.7                | 0.5     | 0.3     | 0.7                |
| TITANIUM DIOXIDE          | 0.5     | 0.5     | 1.0                | 0.5     | 0.4     | 0.6                |
| TALC                      | 0.1     | 0.1     | 0.1                | 0.1     | 0.1     | 0.1                |
| WAX                       | 0.1     | 0.1     | 0.1                | 0.1     | 0.1     | 0.1                |
| CHLORPHEN-IRAMINE MALEATE | —       | 0.27    | 0.81 <sup>a)</sup> | —       | 0.27    | 0.81 <sup>a)</sup> |

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

Some polyols such as sorbitol, maltitol, lactitol, erythritol, or hydrogenated isomaltulose are not sufficiently sweet compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

The formulas listed in Table 31 comprise various sugar-type formulas in which active medicament can be added to gum after it is dissolved in water or mixed with various aqueous solvents. Pseudoephedrine hydrochloride (Sudafed™) is an active medicament used as a nasal decongestant. These formulas give a 3 gram stick with 30 mg of pseudoephedrine hydrochloride.

TABLE 31

| (WEIGHT PERCENT)    |         |         |         |         |         |         |         |         |
|---------------------|---------|---------|---------|---------|---------|---------|---------|---------|
|                     | EX. 230 | EX. 231 | EX. 232 | EX. 233 | EX. 234 | EX. 235 | EX. 236 | EX. 237 |
| SUGAR               | 64.6    | 64.0    | 61.0    | 67.0    | 63.0    | 53.0    | 60.7    | 47.0    |
| BASE                | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    | 19.2    |
| CORN SYRUP          | 12.9    | 10.9    | 8.9     | 2.9     | 6.9     | 6.9     | 0.0     | 2.9     |
| PEPPER-MINT FLAVOR  | 0.9     | 0.9     | 0.9     | 0.9     | 0.9     | 0.0     | 0.9     | 0.9     |
| GLYCERIN            | 1.4     | 0.0     | 0.0     | 0.0     | 0.0     | 0.9     | 1.4     | 0.0     |
| LIQUID/ACTIVE BLEND | 1.0     | 5.0     | 10.0    | 10.0    | 10.0    | 20.0    | 17.8    | 30.0    |

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener are blended into a syrup and applied to pellets. After all coating is applied and dried, talc and wax are added to give a polish. Chlorpheniramine maleate may be applied in a similar manner as in the previous xylitol coating, or may be preblended with the dry charge material.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 30 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, calcium carbonate, magnesium carbonate, starches, gums like dyclonine hydrochloride, gum talha, gum arabic or other

## Example 230

Pseudoephedrine hydrochloride powder can be added directly to the gum.

## Example 231

A 20 gram quantity of pseudoephedrine hydrochloride can be dissolved in 80 grams of water giving a 20% solution and added to gum.

## Example 232

A 10 gram quantity of pseudoephedrine hydrochloride can be dissolved in 50 grams of water and mixed with 50 grams of glycerin and added to the gum.

## Example 233

A 10 gram quantity of pseudoephedrine hydrochloride is mixed with 90 grams of glycerin giving a 10% solution and added to gum.

## Example 234

A 10 gram quantity of pseudoephedrine hydrochloride is mixed with 90 grams of propylene glycol giving a 10% solution and added to gum.

## Example 235

A 10 gram quantity of pseudoephedrine hydrochloride is dissolved in grams of peppermint flavor and added to gum.

## Example 236

A 10 gram quantity of pseudoephedrine hydrochloride is dissolved in 168 grams of corn syrup and added to chewing gum.

## Example 237

To a 200 gram quantity of corn syrup is added 100 grams of glycerin. To this mixture is added 10 gram of pseudoephedrine hydrochloride and blended. This mixture is then added to gum.

In the next examples of sugar formulations, pseudoephedrine hydrochloride can be dissolved in water and emulsifiers can be added to the aqueous solution. Example solutions can be prepared by dissolving 20 grams of pseudoephedrine hydrochloride in 65 grams of water and adding 15 grams of emulsifiers of various hydrophilic-lipophilic balance (HLB) values to the solution. The mixtures can then be used in the following formulas. Example 238 uses a mixture of pseudoephedrine hydrochloride and water with no emulsifier. The HLB value of the emulsifiers used in Examples 238-243 are listed in Table 32.

TABLE 32

|                          | (WEIGHT PERCENT) |         |         |         |         |          |
|--------------------------|------------------|---------|---------|---------|---------|----------|
|                          | EX. 238          | EX. 239 | EX. 240 | EX. 241 | EX. 242 | EX. 243  |
| SUGAR                    | 50.7             | 50.7    | 50.7    | 50.7    | 50.7    | 50.7     |
| BASE                     | 19.2             | 19.2    | 19.2    | 19.2    | 19.2    | 19.2     |
| CORN SYRUP               | 12.9             | 12.9    | 12.9    | 12.9    | 12.9    | 12.9     |
| GLYCERIN                 | 1.4              | 1.4     | 1.4     | 1.4     | 1.4     | 1.4      |
| DEXTROSE                 | 9.9              | 9.9     | 9.9     | 9.9     | 9.9     | 9.9      |
| MONO-HYDRATE             |                  |         |         |         |         |          |
| PEPP. FLAVOR             | 0.9              | 0.9     | 0.9     | 0.9     | 0.9     | 0.9      |
| ACTIVE AGENT             | 5.0              | 5.0     | 5.0     | 5.0     | 5.0     | 5.0      |
| EMULSIFIER/WATER MIXTURE |                  |         |         |         |         |          |
|                          | None             | HLB = 2 | HLB = 4 | HLB = 6 | HLB = 9 | HLB = 12 |

The formulations made in Examples 238-243 can be changed in that the flavor can be mixed together with the aqueous active agent solution and emulsified before adding the mixture to the gum batch.

The following Tables 33 through 40 are examples of gum formulations that demonstrate formula variations in which pseudoephedrine hydrochloride may be used. The active agent may be added with or without encapsulation or may be treated for fast release.

Examples 244-247 in Table 33 demonstrate the use of pseudoephedrine hydrochloride in low-moisture sugar formulations showing less than 2% theoretical moisture:

TABLE 33

|          | (WEIGHT PERCENT) |         |         |         |
|----------|------------------|---------|---------|---------|
|          | EX. 244          | EX. 245 | EX. 246 | EX. 247 |
| SUGAR    | 57.9             | 55.9    | 57.9    | 50.9    |
| GUM BASE | 19.2             | 19.2    | 19.2    | 19.2    |

TABLE 33-continued

|                                       | (WEIGHT PERCENT) |         |         |         |
|---------------------------------------|------------------|---------|---------|---------|
|                                       | EX. 244          | EX. 245 | EX. 246 | EX. 247 |
| CORN <sup>a</sup> SYRUP               | 6.0              | 6.0     | —       | —       |
| DEXTROSE                              | 10.0             | 10.0    | 10.0    | 10.0    |
| MONO-HYDRATE                          |                  |         |         |         |
| LACTOSE                               | 0.0              | 0.0     | 0.0     | 5.0     |
| GLYCERIN <sup>b</sup>                 | 5.0              | 5.0     | 11.0    | 11.0    |
| FLAVOR                                | 0.9              | 0.9     | 0.9     | 0.9     |
| ACTIVE PSEUDO-EPHEDRINE HYDROCHLORIDE | 1.0              | 3.0     | 1.0     | 3.0     |

<sup>a</sup>Corn syrup is evaporated to 85% solids, 15% moisture

<sup>b</sup>Glycerin and syrup may be blended and co-evaporated

Examples 248-251 in Table 34 demonstrate the use of pseudoephedrine hydrochloride in medium-moisture sugar formulations having about 2% to about 5% moisture.

Examples 252-255 in Table 35 demonstrate the use of pseudoephedrine hydrochloride in high-moisture sugar formulations having more than about 5% moisture.

TABLE 34

|                                       | (WEIGHT PERCENT) |         |         |         |
|---------------------------------------|------------------|---------|---------|---------|
|                                       | EX. 248          | EX. 249 | EX. 250 | EX. 251 |
| SUGAR                                 | 52.5             | 50.5    | 52.5    | 49.0    |
| GUM BASE                              | 19.2             | 19.2    | 19.2    | 19.2    |
| CORN SYRUP <sup>a</sup>               | 15.0             | 15.0    | 13.0    | 12.5    |
| DEXTROSE                              | 10.0             | 10.0    | 10.0    | 10.0    |
| MONO-HYDRATE                          |                  |         |         |         |
| GLYCERIN <sup>b</sup>                 | 1.4              | 1.4     | 3.4     | 5.4     |
| FLAVOR                                | 0.9              | 0.9     | 0.9     | 0.9     |
| ACTIVE PSEUDO-EPHEDRINE HYDROCHLORIDE | 1.0              | 3.0     | 1.0     | 3.0     |

<sup>a</sup>Corn syrup is evaporated to 85% solids, 15% moisture

<sup>b</sup>Glycerin and syrup may be blended and co-evaporated



Table 40 shows chewing gum formulations that are free of sugar. These formulations can use a wide variety of other non-sugar alditols.

TABLE 40

|  | (WEIGHT PERCENT) |         |         |         |         |         |         |         |         |         |         |         |
|--|------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|  | EX. 280          | EX. 281 | EX. 282 | EX. 283 | EX. 284 | EX. 285 | EX. 286 | EX. 287 | EX. 288 | EX. 289 | EX. 290 | EX. 291 |
| GUM BASE                               | 25.5             | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    | 25.5    |
| GLYCERIN                               | 8.0              | 8.0     | 8.0     | 8.0     | 8.0     | 2.0     | 8.0     | 8.0     | 8.0     | 2.0     | 8.0     | 2.0     |
| SORBITOL                               | 47.0             | 35.0    | 37.0    | 30.0    | 31.0    | 27.0    | 41.0    | 34.0    | 31.0    | 38.0    | 29.0    | 38.0    |
| MANNITOL                               | —                | 10.0    | 10.0    | 10.0    | 10.0    | 6.0     | 8.0     | 8.0     | 8.0     | —       | —       | —       |
| SORBITOL LIQUID                        | 17.0             | 17.0    | —       | —       | —       | —       | 5.0     | —       | —       | —       | —       | —       |
| LYCASIN                                | —                | —       | 17.0    | 2.0     | 8.0     | 20.0    | —       | 5.0     | 5.0     | 5.0     | 10.0    | 20.0    |
| MALTTTOL                               | —                | —       | —       | 10.0    | —       | —       | —       | 5.0     | —       | —       | —       | —       |
| XYLITOL                                | —                | —       | —       | —       | 15.0    | 15.0    | —       | —       | —       | 15.0    | 15.0    | —       |
| LACTITOL                               | —                | —       | —       | —       | —       | —       | 10.0    | 10.0    | 10.0    | —       | —       | —       |
| PALATINIT                              | —                | —       | —       | —       | —       | —       | —       | —       | 10.0    | 10.0    | 10.0    | 10.0    |
| FLAVOR                                 | 1.5              | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     | 1.5     |
| ACTIVE PSEUDO-EPHEDRINE HYDRO-CHLORIDE | 1.0              | 3.0     | 1.0     | 3.0     | 1.0     | 3.0     | 1.0     | 3.0     | 1.0     | 3.0     | 1.0     | 3.0     |

High-intensity sweeteners (HIS) such as aspartame, acesulfame K, or the salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin, and combinations thereof may be used in any of the Examples listed in Tables 33–40. Since pseudoephedrine hydrochloride may reduce sweetness, HIS may be used in sugar gum, and some of the alditols in sugar-free gum are less sweet than sugar so higher levels of HIS may be needed to obtain the proper level of sweetness.

High-intensity sweeteners (HIS) may also be modified to control their release in those chewing gum formulations. This can be controlled by various methods of encapsulation, agglomeration, absorption, or a combination of methods to obtain either a fast or slow release of the sweetener. Sweetener combinations, some of which may be synergistic, may also be included in the gum formulations.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type-gum center formulations are shown in Table 41 containing pseudoephedrine hydrochloride, which is a nasal decongestant as an active medicament.

TABLE 41

|  | (WEIGHT PERCENT) |         |         |         |         |         |
|--|------------------|---------|---------|---------|---------|---------|
|  | EX. 292          | EX. 293 | EX. 294 | EX. 295 | EX. 296 | EX. 297 |
| SUGAR                                  | 52.0             | 48.0    | 46.5    | 44.0    | 40.0    | 37.5    |
| GUM BASE                               | 26.0             | 30.0    | 35.0    | 26.0    | 30.0    | 35.0    |
| CORN SYRUP                             | 20.0             | 19.0    | 15.00   | 18.0    | 17.0    | 14.00   |
| GLYCERIN                               | 1.0              | 1.0     | 1.00    | 1.0     | 1.0     | 1.00    |
| PEPPERMINT                             | 1.0              | 1.0     | 1.00    | 1.0     | 1.0     | 1.00    |
| FLAVOR                                 | —                | —       | —       | 10.0    | 10.0    | 10.00   |
| DEXTROSE MONO-HYDRATE                  | —                | 1.0     | 1.5     | —       | 1.0     | 1.5     |
| ACTIVE PSEUDO-EPHEDRINE HYDRO-CHLORIDE | —                | —       | —       | —       | —       | —       |

\*All of the active agent is in the coating, which comprises 33% of the product.

Formulations with or without active pseudoephedrine hydrochloride can also be made similar to those found in Tables 33–38 for low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars are polyols may be used in the gum center as found in Tables 39 and 40. Pseudoephedrine hydrochloride may be added to a gum center only, or to a gum coating with none in the center, or to both center and coating. Coated gum pieces are about 1.5 grams per piece, so to obtain 30 mg of pseudoephedrine hydrochloride in two gum pieces, total piece must contain 1.0%.

Pseudoephedrine hydrochloride can be used in the coating formula on the various pellet gum formulations. The fol-

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lowing Table 42 shows some sugar and dextrose type formulas:

TABLE 42

| (DRY WEIGHT PERCENT)           |         |         |                  |         |         |                  |
|--------------------------------|---------|---------|------------------|---------|---------|------------------|
|                                | EX. 298 | EX. 299 | EX. 300          | EX. 301 | EX. 302 | EX. 303          |
| SUGAR                          | 97.1    | 94.4    | 91.1             | 96.9    | 94.1    | 90.6             |
| GUM ARABIC                     | 2.0     | 3.0     | 4.0              | 2.0     | 3.0     | 4.0              |
| TITANIUM DIOXIDE               | 0.5     | 1.0     | 1.0              | —       | —       | —                |
| CALCIUM CARBONATE              | —       | —       | —                | 0.5     | 1.0     | 2.0              |
| FLAVOR                         | 0.3     | 0.5     | 0.8              | 0.5     | 0.8     | 0.3              |
| WAX                            | 0.1     | 0.1     | 0.1              | 0.1     | 0.1     | 0.1              |
| PSEUDO-EPHEDRINE HYDROCHLORIDE | —       | 1.0     | 3.0 <sup>a</sup> | —       | 1.0     | 3.0 <sup>a</sup> |

|                                | EX. 304 | EX. 305 | EX. 306 | EX. 307          |
|--------------------------------|---------|---------|---------|------------------|
| DEXTROSE MONO-HYDRATE          | 97.6    | 94.4    | 96.2    | 91.5             |
| GUM ARABIC                     | 1.5     | 3.0     | 1.5     | 3.0              |
| TITANIUM DIOXIDE               | 0.5     | 1.0     | —       | —                |
| CALCIUM CARBONATE              | —       | —       | 1.0     | 2.0              |
| FLAVOR                         | 0.3     | 0.5     | 0.2     | 0.4              |
| WAX                            | 0.1     | 0.1     | 0.1     | 0.1              |
| PSEUDO-EPHEDRINE HYDROCHLORIDE | —       | 1.0     | 1.0     | 3.0 <sup>a</sup> |

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide or calcium carbonate in this syrup. Pseudoephedrine hydrochloride may be dissolved in water, not mixed with hot syrup, but applied between coatings, or it may be added to the hot syrup and used in the early stages of coating or used throughout the coating process. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. Pseudoephedrine hydrochloride may be dissolved in flavor and added to the coating. After the final coats are applied and dried, wax is applied to give a smooth polish.

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As shown in Table 43, some of the sugar or dextrose may be added as a dry charge, which may also contain the active.

TABLE 43

| (DRY WEIGHT PERCENT)           |         |                  |         |                  |         |                  |
|--------------------------------|---------|------------------|---------|------------------|---------|------------------|
|                                | EX. 308 | EX. 309          | EX. 310 | EX. 311          | EX. 312 | EX. 313          |
| SUGAR                          | 76.5    | 78.4             | —       | —                | 86.5    | —                |
| DEXTROSE MONO-HYDRATE          | —       | —                | 76.5    | 83.3             | —       | 84.1             |
| POWDER                         | 20.0    | 15.0             | —       | —                | —       | —                |
| SUGAR* POWDER                  | —       | —                | 20.0    | 10.0             | —       | —                |
| DEXTROSE* GUM ARABIC           | 2.0     | 3.0              | 2.0     | 3.0              | 8.0     | 8.0              |
| POWDER                         | —       | —                | —       | —                | 4.0     | 4.0              |
| SOLUTION                       | —       | —                | —       | —                | —       | —                |
| FLAVOR                         | 0.4     | 0.5              | 0.4     | 0.6              | 0.4     | 0.8              |
| WAX                            | 0.1     | 0.1              | 0.1     | 0.1              | 0.1     | 0.1              |
| PSEUDO-EPHEDRINE HYDROCHLORIDE | 1.0     | 3.0 <sup>a</sup> | 1.0     | 3.0 <sup>a</sup> | 1.0     | 3.0 <sup>a</sup> |

<sup>a</sup>Powder and/or crystalline sugar may be used.

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product.

In Examples 308–311 gum arabic powder is blended in the sugar syrup. In Examples 312 and 313, gum arabic powder is dry charged after a gum arabic solution is applied in the first stages of coating, then this is followed by a hard shell coating of sugar solution or dextrose solution.

Pseudoephedrine hydrochloride may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations with and without pseudoephedrine hydrochloride similar to those found in Tables 33–38 for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30–46% with the other ingredients proportionally reduced. Some typical gum formulas are in Table 44.

TABLE 44

| (WEIGHT PERCENT)         |         |         |         |         |         |                   |
|--------------------------|---------|---------|---------|---------|---------|-------------------|
|                          | EX. 314 | EX. 315 | EX. 316 | EX. 317 | EX. 318 | EX. 319           |
| GUM BASE                 | 35.0    | 35.0    | 30.0    | 30.0    | 30.0    | 40.0              |
| CALCIUM CARBONATE        | —       | —       | 5.0     | 10.0    | 15.0    | —                 |
| SORBITOL                 | 43.3    | 44.3    | 44.8    | 40.3    | 43.8    | 40.2              |
| MANNITOL                 | 10.0    | 10.0    | 5.0     | 10.0    | —       | 8.0               |
| GLYCERIN                 | —       | 8.0     | 2.0     | —       | 8.0     | 2.0               |
| SORBITOL LIQUID          | 10.0    | —       | 10.0    | 8.0     | —       | 6.0 <sup>a)</sup> |
| FLAVOR                   | 1.5     | 1.5     | 1.5     | 1.5     | 2.0     | 2.0               |
| HIGH INTENSITY SWEETENER | 0.2     | 0.2     | 0.2     | 0.2     | 0.2     | 0.3               |



TABLE 44-continued

| (WEIGHT PERCENT)   |                 |         |         |                 |         |         |                   |
|--|-----------------|---------|---------|-----------------|---------|---------|-------------------|
|  | EX. 314         | EX. 315 | EX. 316 | EX. 317         | EX. 318 | EX. 319 | EX. 320           |
| ACTIVE<br>PSEUDO-<br>EPHEDRINE<br>HYDRO-<br>CHLORIDE <sup>b)</sup> | — <sup>c)</sup> | 1.0     | 1.5     | — <sup>c)</sup> | 1.0     | 1.5     | 2.0 <sup>d)</sup> |

<sup>a)</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid

<sup>b)</sup>This material may be dissolved in water, glycerin, sorbitol liquid, or HSH.

<sup>c)</sup>All of the active agent is in the coating, which comprises 33% of the product.

<sup>d)</sup>This example required 50% of the product to be a coating with no active agent in the coating, to give a gum product with 1% active agent.

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, 20 thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, erythritol, xylitol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels similar to those shown in Table 40. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Pseudoephedrine hydrochloride may be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. The following table gives formulas for a xylitol coating:

TABLE 45

| (DRY WEIGHT PERCENT)                       |         |         |                  |         |         |                  |
|--|---------|---------|------------------|---------|---------|------------------|
|  | EX. 321 | EX. 322 | EX. 323          | EX. 324 | EX. 325 | EX. 326          |
| XYLITOL                                    | 94.8    | 91.4    | 87.7             | 90.1    | 88.9    | 85.8             |
| GUM ARABIC                                 | 4.0     | 6.0     | 7.0              | 8.5     | 8.5     | 10.0             |
| FLAVOR                                     | 0.5     | 0.5     | 0.7              | 0.7     | 0.9     | 0.5              |
| TITANIUM<br>DIOXIDE                        | 0.5     | 0.9     | —                | 0.5     | 0.5**   | 0.5**            |
| TALC                                       | 0.1     | 0.1     | 0.1              | 0.1     | 0.1     | 0.1              |
| WAX  | 0.1     | 0.1     | 0.1              | 0.1     | 0.1     | 0.1              |
| COLOR*                                     | —       | —       | 1.4              | —       | —       | —                |
| PSEUDO-<br>EPHEDRINE<br>HYDRO-<br>CHLORIDE | —       | 1.0     | 3.0 <sup>a</sup> | —       | 1.0     | 3.0 <sup>a</sup> |

\*Lake color dispersed in xylitol solution

\*\*Calcium carbonate used in place of titanium dioxide

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. Pseudoephedrine hydrochloride may be dissolved in water or flavor and added between coating applications or mixed with the hot syrup and used in the early stages of coating or used throughout the coating process. After pellets have been coated and dried, talc and wax are added to give a polish.

For coating formulas based on sorbitol, maltitol, lactitol, erythritol, and hydrogenated isomaltulose, gum arabic can be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols

are more difficult to coat using only a straight syrup, but with proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The following formulations may be used.

TABLE 46

| (DRY WEIGHT PERCENT)                       |         |         |                  |         |         |                  |
|--|---------|---------|------------------|---------|---------|------------------|
|  | EX. 327 | EX. 328 | EX. 329          | EX. 330 | EX. 331 | EX. 332          |
| MALTTITOL                                  | 96.8    | 93.9    | 89.1             | 86.8    | 75.1    | 68.5             |
| MALTTITOL<br>POWDER                        | —       | —       | —                | 10.0    | 20.0    | 25.0             |
| GUM ARABIC                                 | 2.0     | 4.0     | 6.0              | 2.0     | 3.0     | 4.0              |
| FLAVOR                                     | 0.5     | 0.4     | 0.7              | 0.5     | 0.3     | 0.7              |
| TITANIUM<br>DIOXIDE                        | 0.5     | 0.5     | 1.0              | 0.5     | 0.4     | 0.6              |
| TALC                                       | 0.1     | 0.1     | 0.1              | 0.1     | 0.1     | 0.1              |
| WAX  | 0.1     | 0.1     | 0.1              | 0.1     | 0.1     | 0.1              |
| PSEUDO-<br>EPHEDRINE<br>HYDRO-<br>CHLORIDE | —       | 1.0     | 3.0 <sup>a</sup> | —       | 1.0     | 3.0 <sup>a</sup> |

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener are blended into a syrup and applied to pellets. After all coating is applied and dried, talc and wax are added to give a polish. Pseudoephedrine hydrochloride may be applied in a similar manner as in the previous xylitol coating examples, or may be preblended with the dry charge material.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 46 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, calcium carbonate, magnesium carbonate, starches, gums like arabinogalactan, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

Some polyols such as sorbitol, maltitol, lactitol, erythritol, or hydrogenated isomaltulose are not sufficiently sweet

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compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

Liquid flavors generally are not added throughout the coating but at specific points throughout the process. When flavor is added, less air is used for drying until the flavor coating is covered by the next coatings and dried. Flavors may be various spearmint, peppermint, wintergreen, cinnamon, and fruit flavors to yield a wide variety of flavored chewing gum products.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type gum center formulations are shown in Table 47 in which cetyl pyridinium chloride (CPC) can be added as the active medicament. This medicament can be used as an oral antimicrobial to reduce oral malodor and reduce oral bacteria. These formulas give a 1.5 gram piece containing 5 mg of CPC or 0.33%. Gum center formulas may or may not contain CPC, which has been encapsulated for controlled release.

TABLE 47

|                       | (WEIGHT PERCENT) |         |         |                |         |         |
|-----------------------|------------------|---------|---------|----------------|---------|---------|
|                       | EX. 333          | EX. 334 | EX. 335 | EX. 336        | EX. 337 | EX. 338 |
| SUGAR                 | 52.0             | 48.67   | 47.5    | 44.0           | 40.67   | 38.5    |
| GUM BASE              | 26.0             | 30.0    | 35.0    | 26.0           | 30.0    | 35.0    |
| CORN SYRUP            | 20.0             | 19.0    | 15.0    | 18.0           | 17.0    | 14.0    |
| GLYCERIN              | 1.0              | 1.0     | 1.0     | 1.0            | 1.0     | 1.0     |
| PEPPERMINT            | 1.0              | 1.0     | 1.0     | 1.0            | 1.0     | 1.0     |
| FLAVOR                | —                | —       | —       | 10.0           | 10.0    | 10.0    |
| DEXTROSE MONO-HYDRATE | —                | —       | —       | —              | —       | —       |
| ACTIVE CPC            | — <sup>a</sup>   | 0.33    | 0.5     | — <sup>a</sup> | 0.33    | 0.5     |

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product

Formulations with or without CPC can also be made similar to those found in previous tables for low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars and polyols may be used in the gum center as found in previous tables. Cetyl pyridinium chloride may be added to a gum center only, into a gum coating with more in the center or to both center and coating.

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CPC can be used in the coating formula on the various pellet gum formulations. The following Table 48 shows some sugar and dextrose type formulas:

TABLE 48

|                   | (DRY WEIGHT PERCENT) |         |                  |         |         |                  |
|-------------------|----------------------|---------|------------------|---------|---------|------------------|
|                   | EX. 339              | EX. 340 | EX. 341          | EX. 342 | EX. 343 | EX. 344          |
| SUGAR             | 97.1                 | 95.07   | 93.1             | 96.9    | 94.77   | 92.6             |
| GUM ARABIC        | 2.0                  | 3.0     | 4.0              | 2.0     | 3.0     | 4.0              |
| TITANIUM DIOXIDE  | 0.5                  | 1.0     | 1.0              | —       | —       | —                |
| CALCIUM CARBONATE | —                    | —       | —                | 0.5     | 1.0     | 2.0              |
| FLAVOR            | 0.3                  | 0.5     | 0.8              | 0.5     | 0.8     | 0.3              |
| WAX               | 0.1                  | 0.1     | 0.1              | 0.1     | 0.1     | 0.1              |
| CPC               | —                    | 0.33    | 1.0 <sup>a</sup> | —       | 0.33    | 1.0 <sup>a</sup> |

|                       | EX. 345 | EX. 346 | EX. 347 | EX. 348          |
|-----------------------|---------|---------|---------|------------------|
| DEXTROSE MONO-HYDRATE | 97.6    | 95.07   | 96.87   | 93.5             |
| GUM ARABIC            | 1.5     | 3.0     | 1.5     | 3.0              |
| TITANIUM DIOXIDE      | 0.5     | 1.0     | —       | —                |
| CALCIUM CARBONATE     | —       | —       | 1.0     | 2.0              |
| FLAVOR                | 0.3     | 0.5     | 0.2     | 0.4              |
| WAX                   | 0.1     | 0.1     | 0.1     | 0.1              |
| CPC                   | —       | 0.33    | 0.33    | 1.0 <sup>a</sup> |

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide or calcium carbonate in this syrup. CPC may be dissolved in water, not mixed with hot syrup, but applied between coatings, or it may be added to the hot syrup and used in the early stages of coating or used throughout the coating process. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. CPC may also be premixed with the flavor. After the final coats are applied and dried, wax is applied to give a smooth polish.

The above process gives a hard shell coating. Often a dry charge of powdered sugar or dextrose monohydrate may be used. This gives a somewhat softer coating. A dry charge may be used to build up a coating, but then finished with a straight syrup to obtain a hard shell. CPC may be added dry to the coating with the dry charge material. Table 49 gives these types of formulas.

TABLE 49

|                       | (DRY WEIGHT PERCENT) |                  |         |                  |         |                  |
|-----------------------|----------------------|------------------|---------|------------------|---------|------------------|
|                       | EX. 349              | EX. 350          | EX. 351 | EX. 352          | EX. 353 | EX. 354          |
| SUGAR                 | 77.17                | 80.4             | —       | —                | 87.17   | —                |
| DEXTROSE MONO-HYDRATE | —                    | —                | 77.17   | 85.3             | —       | 86.1             |
| POWDER SUGAR*         | 20.0                 | 15.0             | —       | —                | —       | —                |
| POWDER DEXTROSE       | —                    | —                | 20.0    | 10.0             | —       | —                |
| GUM ARABIC            | 2.0                  | 3.0              | 2.0     | 3.0              | 8.0     | 8.0              |
| GUM ARABIC SOLUTION   | —                    | —                | —       | —                | 4.0     | 4.0              |
| FLAVOR                | 0.4                  | 0.5              | 0.4     | 0.6              | 0.4     | 0.8              |
| WAX                   | 0.1                  | 0.1              | 0.1     | 0.1              | 0.1     | 0.1              |
| CPC                   | 0.33                 | 1.0 <sup>a</sup> | 0.33    | 1.0 <sup>a</sup> | 0.33    | 1.0 <sup>a</sup> |

\*Powder and/or crystalline sugar may be used.

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product.

In Examples 349–352, gum arabic is blended in the sugar syrup. In Examples 353 and 354, gum arabic powder is dry charged after gum arabic solution is applied in the first stages of coating, then this is followed by a hard shell coating of sugar solution or dextrose solution.

Cetyl pyridinium chloride may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations with and without cetyl pyridinium chloride similar to those found in previous tables for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30–46% with the other ingredients proportionally reduced. Some typical gum center formulas are in Table 50.

TABLE 50

|                          | (WEIGHT PERCENT) |         |         |                 |         |                   |                    |
|--------------------------|------------------|---------|---------|-----------------|---------|-------------------|--------------------|
|                          | EX. 355          | EX. 356 | EX. 357 | EX. 358         | EX. 359 | EX. 360           | EX. 361            |
| GUM BASE                 | 35.0             | 35.0    | 30.0    | 30.0            | 30.0    | 40.0              | 50.0               |
| CALCIUM CARBONATE        | —                | —       | 5.0     | 10.0            | 15.0    | —                 | —                  |
| SORBITOL                 | 43.3             | 44.97   | 45.8    | 40.3            | 44.47   | 41.2              | 25.84              |
| MANNITOL                 | 10.0             | 10.0    | 5.0     | 10.0            | —       | 8.0               | 10.0               |
| GLYCERIN                 | —                | 8.0     | 2.0     | —               | 8.0     | 2.0               | 2.0                |
| SORBITOL LIQUID          | 10.0             | —       | 10.0    | 8.0             | —       | 6.0 <sup>b)</sup> | 10.0 <sup>b)</sup> |
| FLAVOR                   | 1.5              | 1.5     | 1.5     | 1.5             | 2.0     | 2.0               | 1.3                |
| HIGH INTENSITY SWEETENER | 0.2              | 0.2     | 0.2     | 0.2             | 0.2     | 0.3               | 0.2                |
| CPC <sup>c)</sup>        | — <sup>c)</sup>  | 0.33    | 0.5     | — <sup>c)</sup> | 0.33    | 0.5               | 0.66 <sup>d)</sup> |

<sup>a)</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid.

<sup>b)</sup>This material may be dissolved in water, glycerin, sorbitol liquid, or HSH.

<sup>c)</sup>All of the active agent is in the coating, which comprises 33% of the product.

<sup>d)</sup>This example requires 50% of the product to be a coating with no active agent in the coating, to give a gum product with 0.33% active.

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, xylitol, erythritol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Cetyl pyridinium chloride may be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. The following table gives formulas for a xylitol coating:

TABLE 51

|                  | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|------------------|----------------------|---------|---------|---------|---------|---------|
|                  | EX. 362              | EX. 363 | EX. 364 | EX. 365 | EX. 366 | EX. 367 |
| XYLITOL          | 94.8                 | 92.07   | 89.7    | 90.1    | 89.57   | 87.8    |
| GUM ARABIC       | 4.0                  | 6.0     | 7.0     | 8.5     | 8.5     | 10.0    |
| FLAVOR           | 0.5                  | 0.5     | 0.7     | 0.7     | 0.9     | 0.5     |
| TITANIUM DIOXIDE | 0.5                  | 0.9     | —       | 0.5     | 0.5**   | 0.5**   |
| TALC             | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |

TABLE 51-continued

|       | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|-------|----------------------|---------|---------|---------|---------|---------|
|       | EX. 362              | EX. 363 | EX. 364 | EX. 365 | EX. 366 | EX. 367 |
| WAX   | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| COLOR | —                    | —       | 1.4     | —       | —       | —       |
| CPC   | —                    | 0.33    | 1.0*    | 0.33    | 1.0*    | —       |

\*Lake color dispersed in xylitol solution

\*\*Calcium carbonate used in place of titanium dioxide

\*All of the active agent is in the coating, which comprises 33% of the product.

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. CPC may be dissolved in water or flavor and added between coating applications, or mixed with the hot syrup and used in the early stages of coating or used throughout the coating process. After pellets have been coated and dried, talc and wax are added to give a polish.

For coating formulas based on sorbitol, maltitol, lactitol, erythritol, and hydrogenated isomaltulose, gum arabic can be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols are more difficult to coat using only a straight syrup, but with proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The following formulations may be used.

TABLE 52

|                  | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|------------------|----------------------|---------|---------|---------|---------|---------|
|                  | EX. 368              | EX. 369 | EX. 370 | EX. 371 | EX. 372 | EX. 373 |
| MALTTTOL         | 96.8                 | 94.57   | 91.1    | 86.8    | 75.77   | 68.5    |
| MALTTTOL POWDER  | —                    | —       | —       | 10.0    | 20.0    | 25.0    |
| ARABINO-GALACTAN | 2.0                  | 4.0     | 6.0     | 2.0     | 3.0     | 4.0     |
| FLAVOR           | 0.5                  | 0.4     | 0.7     | 0.5     | 0.3     | 0.7     |

TABLE 52-continued

|                           | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|---------------------------|----------------------|---------|---------|---------|---------|---------|
|                           | EX. 368              | EX. 369 | EX. 370 | EX. 371 | EX. 372 | EX. 373 |
| TITANIUM DIOXIDE          | 0.5                  | 0.5     | 1.0     | 0.5     | 0.4     | 0.6     |
| TALC                      | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX                       | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| CETYL PYRIDINIUM CHLORIDE | —                    | 0.33    | 1.0*    | —       | 0.33    | 1.0*    |

\*All of the active agent is in the coating, which comprises 33% of the product.

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener are blended into a syrup and applied to pellets. After all coating is applied and dried, talc and wax are added to give a polish. Cetyl pyridinium chloride may be applied in a similar manner as in the previous xylitol coating examples, or preblended with the dry charge materials.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 52 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, calcium carbonate, magnesium carbonate, starches, gums like arabinogalactan, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

Some polyols such as sorbitol, maltitol, erythritol, lactitol, or hydrogenated isomaltulose are not sufficiently sweet compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

Liquid flavors generally are not added throughout the coating but at specific points throughout the process. When flavor is added, less air is used for drying until the flavor coating is covered by the next coatings and dried. Flavors may be various spearmint, peppermint, wintergreen, cinnamon, and fruit flavors to yield a wide variety of flavored chewing gum products.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type gum center formulations are shown in Table 53, in which ketoprofen can be added as the active medicament. Ketoprofen is an analgesic to reduce inflammation and pain. These formulas give a 1.5 gram piece containing 12.5 mg of ketoprofen or 0.83% of the total gum product. Gum center formulas may or may not contain encapsulated or controlled release ketoprofen.

TABLE 53

|                       | (WEIGHT PERCENT) |         |         |         |         |         |
|-----------------------|------------------|---------|---------|---------|---------|---------|
|                       | EX. 374          | EX. 375 | EX. 375 | EX. 377 | EX. 378 | EX. 379 |
| SUGAR                 | 52.0             | 48.17   | 46.75   | 44.0    | 40.17   | 37.75   |
| GUM BASE              | 26.0             | 30.0    | 35.0    | 26.0    | 30.0    | 35.0    |
| CORN SYRUP            | 20.0             | 19.0    | 15.0    | 18.0    | 17.0    | 14.0    |
| GLYCERIN              | 1.0              | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     |
| PEPPERMINT FLAVOR     | 1.0              | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     |
| DEXTROSE MONO-HYDRATE | —                | —       | —       | 10.0    | 10.0    | 10.0    |
| KETO-PROFEN           | —*               | 0.83    | 1.25    | —*      | 0.83    | 1.25    |

\*All of the active agent is in the coating, which comprises 33% of the product

Formulations with or without ketoprofen can also be made similar to those found in previous tables for low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars and polyols may be used in the gum center as found in previous tables. Ketoprofen may be added to a gum center only, into a gum coating with none in the center, or to both center and coating.

Ketoprofen can be used in the coating formula on the various pellet gum formulations. The following Table 54 shows some sugar and dextrose type formulas:

TABLE 54

|                   | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|-------------------|----------------------|---------|---------|---------|---------|---------|
|                   | EX. 380              | EX. 381 | EX. 382 | EX. 383 | EX. 384 | EX. 385 |
| SUGAR             | 97.1                 | 94.57   | 91.6    | 96.9    | 94.27   | 91.1    |
| GUM ARABIC        | 2.0                  | 3.0     | 4.0     | 2.0     | 3.0     | 4.0     |
| TITANIUM DIOXIDE  | 0.5                  | 1.0     | 1.0     | —       | —       | —       |
| CALCIUM CARBONATE | —                    | —       | —       | 0.5     | 1.0     | 2.0     |
| FLAVOR            | 0.3                  | 0.5     | 0.8     | 0.5     | 0.8     | 0.3     |
| WAX               | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| KETO-PROFEN       | —                    | 0.83    | 2.5*    | —       | 0.83    | 2.5*    |

|                       | EX. 386 | EX. 387 | EX. 388 | EX. 389 |
|-----------------------|---------|---------|---------|---------|
| DEXTROSE MONO-HYDRATE | 97.6    | 94.57   | 96.37   | 92.0    |
| GUM ARABIC            | 1.5     | 3.0     | 1.5     | 3.0     |
| TITANIUM DIOXIDE      | 0.5     | 1.0     | —       | —       |

TABLE 54-continued

| (DRY WEIGHT PERCENT) |     |      |      |                  |
|----------------------|-----|------|------|------------------|
| CALCIUM CARBONATE    | —   | —    | 1.0  | 2.0              |
| FLAVOR               | 0.3 | 0.5  | 0.2  | 0.4              |
| WAX                  | 0.1 | 0.1  | 0.1  | 0.1              |
| KETO-PROFEN          | —   | 0.83 | 0.83 | 2.5 <sup>a</sup> |

<sup>a</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide or calcium carbonate in this syrup. Ketoprofen may be dissolved in water, not mixed with hot syrup, but applied between coatings, or it may be added to the hot syrup and used in the early stages of coating or used throughout the coating process. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. Ketoprofen may also be premixed with the flavor. After the final coats are applied and dried, wax is applied to give a smooth polish.

The above process gives a hard shell coating. Often a dry charge of powdered sugar or dextrose monohydrate may be used. This gives a somewhat softer coating. A dry charge, which also may contain the active, may be used to build up a coating, but then finished with a straight syrup to obtain a hard shell. Table 55 gives these types of formulas.

TABLE 55-continued

| (DRY WEIGHT PERCENT) |         |                  |         |                  |         |                  |
|----------------------|---------|------------------|---------|------------------|---------|------------------|
|                      | EX. 390 | EX. 391          | EX. 392 | EX. 393          | EX. 394 | EX. 395          |
| GUM ARABIC POWDER    | 2.0     | 3.0              | 2.0     | 3.0              | 8.0     | 8.0              |
| GUM ARABIC SOLUTION  | —       | —                | —       | —                | 4.0     | 4.0              |
| FLAVOR               | 0.4     | 0.5              | 0.4     | 0.6              | 0.4     | 0.8              |
| WAX                  | 0.1     | 0.1              | 0.1     | 0.1              | 0.1     | 0.1              |
| KETO-PROFEN          | 0.83    | 2.5 <sup>a</sup> | 0.83    | 2.5 <sup>a</sup> | 0.83    | 2.5 <sup>a</sup> |

<sup>a</sup>Powder and/or crystalline sugar may be used.

<sup>b</sup>All of the active agent is in the coating, which comprises 33% of the product.

In Examples 390–393, gum arabic is blended in the sugar syrup. In Examples 394 and 395, gum arabic powder is dry charged after gum arabic solution is applied in the first stages of coating, then this is followed by a hard shell coating of sugar solution or dextrose solution.

Ketoprofen may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations with and without ketoprofen similar to those found in previous tables for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30–46% with the other ingredients proportionally reduced. Some typical gum formulas are in Table 56.

TABLE 56

| (WEIGHT PERCENT)         |                |         |         |                |         |                  |                   |
|--------------------------|----------------|---------|---------|----------------|---------|------------------|-------------------|
|                          | EX. 396        | EX. 397 | EX. 398 | EX. 399        | EX. 400 | EX. 401          | EX. 402           |
| GUM BASE                 | 35.0           | 35.0    | 30.0    | 30.0           | 30.0    | 40.0             | 50.0              |
| CALCIUM CARBONATE        | —              | —       | 5.0     | 10.0           | 15.0    | —                | —                 |
| SORBITOL                 | 43.3           | 44.47   | 45.05   | 40.3           | 43.97   | 40.45            | 24.83             |
| MANNITOL                 | 10.0           | 10.0    | 5.0     | 10.0           | —       | 8.0              | 10.0              |
| GLYCERIN                 | —              | 8.0     | 2.0     | —              | 8.0     | 2.0              | 2.0               |
| SORBITOL LIQUID          | 10.0           | —       | 10.0    | 8.0            | —       | 6.0 <sup>b</sup> | 10.0 <sup>b</sup> |
| FLAVOR                   | 1.5            | 1.5     | 1.5     | 1.5            | 2.0     | 2.0              | 1.3               |
| HIGH INTENSITY SWEETENER | 0.2            | 0.2     | 0.2     | 0.2            | 0.2     | 0.3              | 0.2               |
| KETOPROFEN <sup>c</sup>  | — <sup>d</sup> | 0.83    | 1.25    | — <sup>d</sup> | 0.83    | 1.25             | 1.67 <sup>d</sup> |

<sup>a</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid.

<sup>b</sup>Ketoprofen may be dissolved in water, glycerin, sorbitol liquid, or HSH, or flavor.

<sup>c</sup>All of the active agent is in the coating, which comprises 33% of the product.

<sup>d</sup>This example requires 50% of the product to be a coating with no active agent in the coating, to give a gum product with 0.83% active agent.

TABLE 55

| (DRY WEIGHT PERCENT)  |         |         |         |         |         |         |
|-----------------------|---------|---------|---------|---------|---------|---------|
|                       | EX. 390 | EX. 391 | EX. 392 | EX. 393 | EX. 394 | EX. 395 |
| SUGAR                 | 76.67   | 78.9    | —       | —       | 66.67   | —       |
| DEXTROSE MONO-HYDRATE | —       | —       | 76.67   | 83.8    | —       | 84.6    |
| POWDER                | 20.0    | 15.0    | —       | —       | —       | —       |
| SUGAR* POWDER         | —       | —       | 20.0    | 10.0    | —       | —       |
| DEXTROSE*             | —       | —       | —       | —       | —       | —       |

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, xylitol, erythritol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Ketoprofen may be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltu-

lose and erythritol. The following table gives formulas for a xylitol coating:

TABLE 57

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 403 | EX. 404 | EX. 405 | EX. 406 | EX. 407 | EX. 408 |
| XYLITOL              | 94.8    | 91.57   | 88.2    | 90.1    | 89.07   | 86.3    |
| GUM ARABIC           | 4.0     | 6.0     | 7.0     | 8.5     | 8.5     | 10.0    |
| FLAVOR               | 0.5     | 0.5     | 0.7     | 0.7     | 0.9     | 0.5     |
| TITANIUM DIOXIDE     | 0.5     | 0.9     | —       | 0.5     | 0.5**   | 0.5**   |
| TALC                 | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| COLOR*               | —       | —       | 1.4     | —       | —       | —       |
| KETO-PROFEN          | —       | 0.83    | 2.5*    | —       | 0.83    | 2.5*    |

\*Lake color dispersed in xylitol solution.

Calcium carbonate used in place of titanium dioxide.

\*All of the active agent is in the coating, which comprises 33% of the product.

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. After pellets have been coated and dried, talc and wax are added to give a polish. Ketoprofen may be dissolved in water or flavor and added between coating applications, or mixed with the hot syrup and used in the early stages of coating or used throughout the coating process.

For coating formulas based on sorbitol, maltitol, lactitol, erythritol, and hydrogenated isomaltulose, gum arabic can be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols are more difficult to coat using only a straight syrup, but with proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The following formulations may be used.

TABLE 58

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 409 | EX. 410 | EX. 411 | EX. 412 | EX. 413 | EX. 414 |
| MALTTITOL            | 96.8    | 94.07   | 89.6    | 86.8    | 75.27   | 67.0    |
| MALTTITOL POWDER     | —       | —       | —       | 10.0    | 20.0    | 25.0    |
| GUM ARABIC           | 2.0     | 4.0     | 6.0     | 2.0     | 3.0     | 4.0     |
| FLAVOR               | 0.5     | 0.4     | 0.7     | 0.5     | 0.3     | 0.7     |
| TITANIUM DIOXIDE     | 0.5     | 0.5     | 1.0     | 0.5     | 0.4     | 0.6     |
| TALC                 | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| KETO-PROFEN          | —       | 0.83    | 2.5*    | —       | 0.83    | 2.5*    |

\*All of the active agent is in the coating, which comprises 33% of the product.

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener are blended into a syrup and applied to pellets. After all coating is applied and dried, talc and wax are added to give a polish. Ketoprofen may be applied in a similar manner as in the previous xylitol coating examples, or preblended with the dry charge material and added to the coating.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 58 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky

during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, calcium carbonate, magnesium carbonate, starches, gums like arabinogalactan, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

Some polyols such as sorbitol, maltitol, erythritol, lactitol, or hydrogenated isomaltulose are not sufficiently sweet compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type gum center formulations are shown in Table 59 in which dextromethorphan hydrobromide can be added as the active medicament. This material is an antitussive for cough relief. These formulas give a 1.5 gram piece containing 15 mg of dextromethorphan hydrobromide or 1.0% of gum product. Gum centers may or may not contain dextromethorphan hydrobromide.

TABLE 59

| (WEIGHT PERCENT)      |         |         |         |         |         |         |
|-----------------------|---------|---------|---------|---------|---------|---------|
|                       | EX. 415 | EX. 416 | EX. 417 | EX. 418 | EX. 419 | EX. 420 |
| SUGAR                 | 52.0    | 48.0    | 46.5    | 44.0    | 40.0    | 37.5    |
| GUM BASE              | 26.0    | 30.0    | 35.0    | 26.0    | 30.0    | 35.0    |
| CORN SYRUP            | 20.0    | 19.0    | 15.0    | 18.0    | 17.0    | 14.0    |
| GLYCERIN              | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     |
| PEPPERMINT FLAVOR     | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     |
| DEXTROSE MONO-HYDRATE | —       | —       | —       | 10.0    | 10.0    | 10.0    |
| DEXTROMETHORPHAN HBr  | —*      | 1.0     | 1.5     | —*      | 1.0     | 1.5     |

Formulations with or without Dextromethorphan HBr can also be made similar to those found previously in Tables for

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low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars and polyols may be used in the gum center as found in previous tables. Dextromethorphan HBr may be added to the gum center only, into a gum coating with none in the center, or both center and coating.

Dextromethorphan HBr can then be used in the coating formula on the various pellet gum formulations. The following Table 60 shows some sugar and dextrose type formulas:

TABLE 60

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 421 | EX. 422 | EX. 423 | EX. 424 | EX. 425 | EX. 426 |
| SUGAR                | 97.1    | 94.4    | 91.1    | 96.9    | 94.1    | 90.6    |
| GUM ARABIC           | 2.0     | 3.0     | 4.0     | 2.0     | 3.0     | 4.0     |
| TITANIUM DIOXIDE     | 0.5     | 1.0     | 1.0     | —       | —       | —       |
| CALCIUM CARBONATE    | —       | —       | —       | 0.5     | 1.0     | 2.0     |
| FLAVOR               | 0.3     | 0.5     | 0.8     | 0.5     | 0.8     | 0.3     |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| DEXTROMETHORPHAN HBr | —       | 1.0     | 3.0*    | —       | 1.0     | 3.0*    |

|                       | EX. 427 | EX. 428 | EX. 429 | EX. 430 |
|-----------------------|---------|---------|---------|---------|
| DEXTROSE MONO-HYDRATE | 97.6    | 94.4    | 96.2    | 91.5    |
| GUM ARABIC            | 1.5     | 3.0     | 1.5     | 3.0     |
| TITANIUM DIOXIDE      | 0.5     | 1.0     | —       | —       |
| CALCIUM CARBONATE     | —       | —       | 1.0     | 2.0     |
| FLAVOR                | 0.3     | 0.5     | 0.2     | 0.4     |
| WAX                   | 0.1     | 0.1     | 0.1     | 0.1     |
| DEXTROMETHORPHAN HBr  | —       | 1.0     | 1.0     | 3.0*    |

\*All of the active agent is in the coating which comprises 33% of the product.

The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide or calcium carbonate in this syrup. Dextromethorphan HBr may be dissolved in water, not mixed with hot syrup, but applied between coatings, or it may be added to the hot syrup and used in the early stages of coating or used throughout the coating process. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. Dextrometho-

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phan HBr may also be premixed with the flavor. After the final coats are applied and dried, wax is applied to give a smooth polish.

The above process gives a hard shell coating. Often a dry charge of powdered sugar or dextrose monohydrate may be used. This gives a somewhat softer coating. A dry charge may be used to build up a coating, but then finished with a straight syrup to obtain a hard shell. Dextromethorphan HBr may also be added to the dry charge material. Table 61 gives these types of formulas.

TABLE 61

| (DRY WEIGHT PERCENT)  |         |         |         |         |         |         |
|-----------------------|---------|---------|---------|---------|---------|---------|
|                       | EX. 431 | EX. 432 | EX. 433 | EX. 434 | EX. 435 | EX. 436 |
| SUGAR                 | 76.5    | 78.4    | —       | —       | 86.5    | —       |
| DEXTROSE MONO-HYDRATE | —       | —       | 76.5    | 83.3    | —       | 84.1    |
| POWDER                | 20.0    | 15.0    | —       | —       | —       | —       |
| SUGAR* POWDER         | —       | —       | 20.0    | 10.0    | —       | —       |
| DEXTROSE* GUM ARABIC  | 2.0     | 3.0     | 2.0     | 3.0     | 8.0     | 8.0     |
| POWDER                | —       | —       | —       | —       | 4.0     | 4.0     |
| GUM ARABIC SOLUTION   | —       | —       | —       | —       | —       | —       |
| FLAVOR                | 0.4     | 0.5     | 0.4     | 0.6     | 0.4     | 0.8     |
| WAX                   | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| DEXTROMETHORPHAN HBr  | 1.0     | 3.0*    | 1.0     | 3.0*    | 1.0     | 3.0*    |

\*Powder and/or crystalline sugar may be used.

\*All of the active agent is in the coating, which comprises 33% of the product.

In Examples 431–434 gum arabic is blended in the sugar syrup. In Examples 435 and 436, gum arabic powder is dry charged after a gum arabic solution is applied in the first stages of coating, then this is followed by a hard shell coating of sugar solution or dextrose solution.

Dextromethorphan HBr may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations with and without Dextromethorphan HBr similar to those found in previous tables for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30–46% with the other ingredients proportionally reduced. Some typical gum center formulas are in Table 62.

TABLE 62

| (WEIGHT PERCENT)  |         |         |         |         |         |                   |
|-------------------|---------|---------|---------|---------|---------|-------------------|
|                   | EX. 437 | EX. 438 | EX. 439 | EX. 440 | EX. 441 | EX. 442           |
| GUM BASE          | 35.0    | 35.0    | 30.0    | 30.0    | 30.0    | 40.0              |
| CALCIUM CARBONATE | —       | —       | 5.0     | 10.0    | 15.0    | —                 |
| SORBITOL          | 43.3    | 44.3    | 43.3    | 40.3    | 43.8    | 38.7              |
| MANNITOL          | 10.0    | 10.0    | 5.0     | 10.0    | —       | 8.0               |
| GLYCERIN          | —       | 8.0     | 2.0     | —       | 8.0     | 2.0               |
| SORBITOL LIQUID   | 10.0    | —       | 10.0    | 8.0     | —       | 6.0 <sup>b)</sup> |
| FLAVOR            | 1.5     | 1.5     | 1.5     | 1.5     | 2.0     | 2.0               |

1.3



TABLE 62-continued

|                                     | (WEIGHT PERCENT) |         |         |                 |         |         |                   |
|-------------------------------------|------------------|---------|---------|-----------------|---------|---------|-------------------|
|                                     | EX. 437          | EX. 438 | EX. 439 | EX. 440         | EX. 441 | EX. 442 | EX. 443           |
| HIGH INTENSITY SWEETENER            | 0.2              | 0.2     | 0.2     | 0.2             | 0.2     | 0.3     | 0.2               |
| DEXTRO-METHORPHAN HBr <sup>b)</sup> | — <sup>c)</sup>  | 1.0     | 3.0     | — <sup>c)</sup> | 1.0     | 3.0     | 2.0 <sup>d)</sup> |

<sup>a)</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid

<sup>b)</sup>Dextromethorphan HBr may be dissolved in water, glycerin, sorbitol liquid, HSH, or flavor

<sup>c)</sup>All of the active agent is in the coating, which comprises 33% of the product

<sup>d)</sup>This example requires 50% of the product to be a coating with no active agent in the coating, to give a gum product with 1% active agent.

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, xylitol, erythritol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Dextromethorphan may be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. The following table gives formulas for a xylitol coating:

TABLE 63

|                       | (DRY WEIGHT PERCENT) |         |                   |         |         |                   |
|-----------------------|----------------------|---------|-------------------|---------|---------|-------------------|
|                       | EX. 444              | EX. 445 | EX. 446           | EX. 447 | EX. 448 | EX. 449           |
| XYLITOL               | 94.8                 | 91.4    | 87.7              | 90.1    | 88.9    | 85.8              |
| GUM ARABIC            | 4.0                  | 6.0     | 7.0               | 8.5     | 8.5     | 10.0              |
| FLAVOR                | 0.5                  | 0.5     | 0.7               | 0.7     | 0.9     | 0.5               |
| TITANIUM DIOXIDE      | 0.5                  | 0.9     | —                 | 0.5     | 0.5**   | 0.5**             |
| TALC                  | 0.1                  | 0.1     | 0.1               | 0.1     | 0.1     | 0.1               |
| WAX                   | 0.1                  | 0.1     | 0.1               | 0.1     | 0.1     | 0.1               |
| COLOR*                | —                    | —       | 1.4               | —       | —       | —                 |
| DEXTRO-METHORPHAN HBr | —                    | 1.0     | 3.0 <sup>a)</sup> | —       | 1.0     | 3.0 <sup>a)</sup> |

\*Lake color dispersed in xylitol solution

\*\*Calcium carbonate used in place of titanium dioxide

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. After pellets have been coated and dried, talc and wax are added to give a polish. Dextromethorphan HBr may be dissolved in water or flavor and added between coating applications, or mixed with hot syrup and used in the early stages of coating or used throughout the coating process.

For coating formulas based on sorbitol, maltitol, lactitol, erythritol, and hydrogenated isomaltulose, gum arabic can be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols are more difficult to coat using only a straight syrup, but with

proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The active may be premixed with the dry charge material. The following formulations may be used.

TABLE 64

|                       | (DRY WEIGHT PERCENT) |         |                   |         |         |                   |
|-----------------------|----------------------|---------|-------------------|---------|---------|-------------------|
|                       | EX. 450              | EX. 451 | EX. 452           | EX. 453 | EX. 454 | EX. 455           |
| MALTTITOL             | 96.8                 | 93.9    | 89.1              | 91.8    | 85.1    | 76.5              |
| MALTTITOL POWDER      | —                    | —       | —                 | 5.0     | 10.0    | 15.0              |
| GUM ARABIC            | 2.0                  | 4.0     | 6.0               | 2.0     | 3.0     | 4.0               |
| FLAVOR                | 0.5                  | 0.4     | 0.7               | 0.5     | 0.3     | 0.7               |
| TITANIUM DIOXIDE      | 0.5                  | 0.5     | 1.0               | 0.5     | 0.4     | 0.6               |
| TALC                  | 0.1                  | 0.1     | 0.1               | 0.1     | 0.1     | 0.1               |
| WAX                   | 0.1                  | 0.1     | 0.1               | 0.1     | 0.1     | 0.1               |
| DEXTRO-METHORPHAN HBr | —                    | 1.0     | 3.0 <sup>a)</sup> | —       | 1.0     | 3.0 <sup>a)</sup> |

<sup>a)</sup>All of the active agent is in the coating, which comprises 33% of the product.

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener is blended into a syrup and applied to pellets. After all coating is applied and dried, talc and wax are added to give a polish. Dextromethorphan may be applied in a similar manner as the previous xylitol examples, or added with the dry charge material.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 64 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, calcium carbonate, magnesium carbonate, starches, gums like arabinogalactan, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

Some polyols such as sorbitol, maltitol, erythritol, lactitol, or hydrogenated isomaltulose are not sufficiently sweet

compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

As noted earlier, the gum formulas can be prepared as stick or tab products in the sugar or sugarless type formulations. These formulas can also be made in a pellet or pillow shape pellet or a round ball or any other shape of product for coating/panning. However, gum formulas are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

As a result, gum centers are usually formulated with about 25% to about 40% gum base with a corresponding decrease in the other ingredients except flavor. Generally flavors increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

Some typical sugar type gum center formulations are shown in Table 65 that can be used as centers that are coated with calcium carbonate to give an effective antacid.

TABLE 65

| (WEIGHT PERCENT) |         |         |         |         |         |         |
|------------------|---------|---------|---------|---------|---------|---------|
|                  | EX. 456 | EX. 457 | EX. 458 | EX. 459 | EX. 460 | EX. 461 |
| SUGAR            | 48.0    | 48.0    | 46.0    | 40.0    | 39.0    | 36.0    |
| GUM BASE         | 30.0    | 35.0    | 40.0    | 30.0    | 35.0    | 40.0    |
| CORN SYRUP       | 20.0    | 15.0    | 12.0    | 18.0    | 14.0    | 12.0    |
| GLYCERIN         | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     |
| PEPPERMINT       | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     | 1.0     |
| FLAVOR           |         |         |         |         |         |         |
| DEXTROSE         | —       | —       | —       | 10.0    | 10.0    | 10.0    |
| MONO-HYDRATE     |         |         |         |         |         |         |

Formulations can also be made similar to those found in previous tables for low, medium, and high moisture formulas. Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars may be used in the gum center as found in previous tables.

Calcium carbonate can then be used in the coating formula on the various pellet gum formulations. The following Table 66 shows some sugar and dextrose type formulas: Using a 1 gram center, the levels of calcium carbonate in the following tables will give 250–800 mg per 2 pieces in 1.5–3.0 gum pieces with 33 to 50% coating.

TABLE 66

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 462 | EX. 463 | EX. 464 | EX. 465 | EX. 466 | EX. 467 |
| SUGAR                | 72.1    | 65.4    | 54.1    | 72.4    | 66.1    | 55.6    |
| GUM ARABIC           | 2.0     | 3.0     | 4.0     | 2.0     | 3.0     | 4.0     |
| TITANIUM             | 0.5     | 1.0     | 1.0     | —       | —       | —       |
| DIOXIDE              |         |         |         |         |         |         |
| CALCIUM              | 25.0    | 30.0    | 40.0    | 25.0    | 30.0    | 40.0    |
| CARBONATE            |         |         |         |         |         |         |

TABLE 66—continued

| (DRY WEIGHT PERCENT) |         |         |         |         |     |     |
|----------------------|---------|---------|---------|---------|-----|-----|
|                      | EX. 468 | EX. 469 | EX. 470 | EX. 471 |     |     |
| FLAVOR               | 0.3     | 0.5     | 0.8     | 0.5     | 0.8 | 0.3 |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1 | 0.1 |
| DEXTROSE             | 72.6    | 55.4    | 73.2    | 56.5    |     |     |
| MONO-HYDRATE         |         |         |         |         |     |     |
| GUM ARABIC           | 1.5     | 3.0     | 1.5     | 3.0     |     |     |
| TITANIUM             | 0.5     | 1.0     | —       | —       |     |     |
| DIOXIDE              |         |         |         |         |     |     |
| CALCIUM              | 25.0    | 40.0    | 25.0    | 40.0    |     |     |
| CARBONATE            |         |         |         |         |     |     |
| FLAVOR               | 0.3     | 0.5     | 0.2     | 0.4     |     |     |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     |     |     |

The above formulations are made by making a syrup by dissolving the sugar and gum arabic in solution at about 75% solids at boiling, and suspending titanium dioxide and/or calcium carbonate in this syrup. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. After the final coats are applied and dried, wax is applied to give a smooth polish.

The above process gives a hard shell coating. Often a dry charge of powdered sugar or dextrose monohydrate may be used. This gives a somewhat softer coating. A dry charge may be used to build up a coating, but then finished with a straight syrup to obtain a hard shell. Table 67 gives these types of formulas.

TABLE 67

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 472 | EX. 473 | EX. 474 | EX. 475 | EX. 476 | EX. 477 |
| SUGAR                | 62.5    | 51.4    | —       | —       | 52.5    | —       |
| DEXTROSE             | —       | —       | 62.5    | 51.3    | —       | 42.1    |
| MONO-HYDRATE         |         |         |         |         |         |         |
| POWDER               | 10.0    | 5.0     | —       | —       | —       | —       |
| SUGAR*               | —       | —       | 10.0    | 5.0     | 10.0    | 5.0     |
| POWDER               | —       | —       | 10.0    | 5.0     | 10.0    | 5.0     |
| DEXTROSE*            | 2.0     | 3.0     | 2.0     | 3.0     | 8.0     | 8.0     |
| GUM ARABIC           | —       | —       | —       | —       | 4.0     | 4.0     |
| POWDER*              | —       | —       | —       | —       | 4.0     | 4.0     |
| GUM ARABIC           | —       | —       | —       | —       | 4.0     | 4.0     |
| SOLUTION             |         |         |         |         |         |         |
| FLAVOR               | 0.4     | 0.5     | 0.4     | 0.6     | 0.4     | 0.8     |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| CALCIUM              | 25.0    | 40.0    | 25.0    | 40.0    | 25.0    | 40.0    |
| CARBONATE            |         |         |         |         |         |         |

\*Powder and/or crystalline sugar along with gum arabic may be blended with calcium carbonate, or calcium carbonate may be suspended in the sugar or dextrose syrup.

In Examples 472–475, gum arabic is blended in the sugar syrup; In Examples 476 and 477, gum arabic powder is dry charged after a gum arabic solution is applied in the first stages of coating, then this is followed by a hard shell coating of sugar solution or dextrose solution.

Gum arabic may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Formulations similar to those found in previous tables for low and high moisture gum can be used to make gum centers. Generally, the base level may be increased to 30–46% with the other ingredients proportionally reduced. Some typical gum formulas are in Table 68.

TABLE 68

|                                 | (WEIGHT PERCENT) |         |         |         |         |                   |                    |
|---------------------------------|------------------|---------|---------|---------|---------|-------------------|--------------------|
|                                 | EX. 478          | EX. 479 | EX. 480 | EX. 481 | EX. 482 | EX. 483           | EX. 484            |
| GUM BASE                        | 35.0             | 35.0    | 30.0    | 30.0    | 30.0    | 40.0              | 30.0               |
| CALCIUM CARBONATE <sup>b)</sup> | —                | —       | 5.0     | 10.0    | 10.0    | —                 | —                  |
| SORBITOL                        | 43.3             | 45.3    | 46.3    | 40.3    | 49.8    | 41.7              | 46.5               |
| MANNITOL                        | 10.0             | 10.0    | 5.0     | 10.0    | —       | 8.0               | 10.0               |
| GLYCERIN                        | —                | 8.0     | 2.0     | —       | 8.0     | 2.0               | 2.0                |
| SORBITOL LIQUID                 | 10.0             | —       | 10.0    | 8.0     | —       | 6.0 <sup>a)</sup> | 10.0 <sup>a)</sup> |
| FLAVOR                          | 1.5              | 1.5     | 1.5     | 1.5     | 2.0     | 2.0               | 1.3                |
| HIGH INTENSITY SWEETENER        | 0.2              | 0.2     | 0.2     | 0.2     | 0.2     | 0.3               | 0.2                |

<sup>a)</sup>Lycasin brand hydrogenated starch hydrolyzate used instead of sorbitol liquid

<sup>b)</sup>This material is base filler and may not release to give an anticid effect.

In the above center formulations, the high intensity sweetener used is aspartame. However other high intensity sweetener such as alitame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcone, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

Lycasin and other polyols such as maltitol, xylitol, erythritol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels similar to those shown previously. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high intensity sweetener.

Calcium carbonate can be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. Gum arabic acts as a binder, film former, hardener of the coated pellet. The following table gives formulas for a xylitol coating:

TABLE 69

|                   | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|-------------------|----------------------|---------|---------|---------|---------|---------|
|                   | EX. 485              | EX. 486 | EX. 487 | EX. 488 | EX. 489 | EX. 490 |
| XYLITOL           | 69.8                 | 52.4    | 65.7    | 50.6    | 65.4    | 49.3    |
| GUM ARABIC        | 4.0                  | 6.0     | 7.0     | 8.5     | 8.5     | 10.0    |
| FLAVOR            | 0.5                  | 0.5     | 0.7     | 0.7     | 0.9     | 0.5     |
| TITANIUM DIOXIDE  | 0.5                  | 0.9     | —       | —       | —       | —       |
| TALC              | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX               | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| COLOR*            | —                    | —       | 1.4     | —       | —       | —       |
| CALCIUM CARBONATE | 25.0                 | 40.0    | 25.0    | 40.0    | 25.0    | 40.0    |

\*Lake color dispersed in xylitol solution

The above formulas are used to coat pellets by applying a xylitol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. Calcium carbonate may be suspended in the xylitol hot syrup or added as a dry powder between syrup applications. After pellets have been coated and dried, talc and wax are added to give a polish.

Like xylitol, erythritol coating also requires a binder, film former, and hardener in the coating to make an acceptable product. The following formulations can be made:

TABLE 70

|                   | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|-------------------|----------------------|---------|---------|---------|---------|---------|
|                   | EX. 491              | EX. 492 | EX. 493 | EX. 494 | EX. 495 | EX. 496 |
| ERYTHRITOL        | 68.8                 | 51.5    | 64.2    | 50.1    | 63.4    | 46.8    |
| GUM ARABIC        | 5.0                  | 7.0     | 8.5     | 8.5     | 10.0    | 12.0    |
| FLAVOR            | 0.5                  | 0.4     | 0.7     | 0.7     | 0.9     | 0.5     |
| TITANIUM DIOXIDE  | 0.5                  | 0.9     | —       | 0.5     | 0.5     | 0.5     |
| TALC              | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX               | 0.1                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| COLOR*            | —                    | —       | 1.4*    | —       | —       | —       |
| CALCIUM CARBONATE | 25.0                 | 40.0    | 25.0    | 40.0    | 25.0    | 40.0    |

\*Lake color dispersed in erythritol solution

The above formulas are used to coat pellets by applying a erythritol/gum arabic solution in multiple coats and air drying. Color or whitener is also mixed in the solution. Calcium carbonate may be suspended in the hot erythritol syrup or added as a dry powder between syrup applications. After pellets have been coated and dried, talc and wax are added to give a polish.

For coating formulas based on sorbitol, maltitol, lactitol, and hydrogenated isomaltulose, gum arabic can be used as a binder and film former, and a crystallization modifier to help facilitate coating. Generally these polyols are more difficult to coat using only a straight syrup, but with proper technique a good smooth hard shell can be made. However, it may be preferable to add a dry charge to quicken the drying process before the pellets get too sticky. The following formulations may be used.

TABLE 71

|                 | (DRY WEIGHT PERCENT) |         |         |         |         |         |
|-----------------|----------------------|---------|---------|---------|---------|---------|
|                 | EX. 497              | EX. 498 | EX. 499 | EX. 500 | EX. 501 | EX. 502 |
| MALTITOL        | 71.8                 | 54.9    | 67.1    | 51.8    | 61.1    | 39.5    |
| MALTITOL POWDER | —                    | —       | —       | 5.0     | 10.0    | 15.0    |
| GUM ARABIC      | 2.0                  | 4.0     | 6.0     | 2.0     | 3.0     | 4.0     |
| FLAVOR          | 0.5                  | 0.4     | 0.7     | 0.5     | 0.3     | 0.7     |

TABLE 71-continued

| (DRY WEIGHT PERCENT) |         |         |         |         |         |         |
|----------------------|---------|---------|---------|---------|---------|---------|
|                      | EX. 497 | EX. 498 | EX. 499 | EX. 500 | EX. 501 | EX. 502 |
| TITANIUM DIOXIDE     | 0.5     | 0.5     | 1.0     | 0.5     | 0.4     | 0.6     |
| TALC                 | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| WAX                  | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     | 0.1     |
| CALCIUM CARBONATE    | 25.0    | 40.0    | 25.0    | 40.0    | 25.0    | 40.0    |

Maltitol powder is used to dry charge in the early stages of coating. Maltitol, gum arabic, and whitener is blended into a syrup and applied to pellets. Calcium carbonate may be applied with the syrup suspension, preblended with powder maltitol or added as a dry charge. After all coating is applied and dried, talc and wax are added to give a polish.

In a similar manner, coatings with sorbitol, lactitol, and hydrogenated isomaltulose may be made in the coating formulas in Table 71 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum arabic could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would only be used in the early stages of the coating process.

In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, magnesium carbonate, starches, gums like arabinogalactan, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

Some polyols such as sorbitol, maltitol, lactitol, or hydrogenated isomaltulose are not sufficiently sweet compared to sugar or xylitol, so high intensity sweeteners may be added to the coating, such as aspartame, acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcone, glycyrrhizin, neotame, and combinations thereof. If a hot syrup is applied, heat may degrade the sweetener so only stable sweeteners should be used. Generally high intensity sweeteners are added with the polyol/gum arabic solution to obtain an even distribution in the coatings.

Liquid flavors generally are not added throughout the coating but at specific points throughout the process. When flavor is added, less air is used for drying until the flavor coating is covered by the next coatings and dried. Flavors may be various spearmint, peppermint, wintergreen, cinnamon, and fruit flavors to yield a wide variety of flavored chewing gum products.

It should be appreciated that the compositions and methods of the present invention are capable of being incorporated in the form of a variety of embodiments, only a few of which have been illustrated and described above. The invention may be embodied in other forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

1. A method of producing a chewing gum product containing a physically-modified active agent in order to control the release rate of the active agent comprising the steps of:

5 a) mixing a quantity of an active agent, which comprises one or more materials selected from the group consisting of benzooin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lecithin, lycopene, polyphenol, psyllium, chromium picolinate and phenylpropanolamine, with a modifying agent and a high-potency sweetener selected from the group consisting of neotame, aspartame, alitame, salts of acesulfame, cyclamate and its salts, saccharin and its salts, thaumatin, monellin, dihydrochalcones, sucralose and combinations thereof, to form a modified release rate active agent and high-potency sweetener combination;

b) adding a quantity of the combination to a chewing gum formulation to provide an effective amount of the active agent in the chewing gum formulation.

2. The method of claim 1 wherein said modifying agent is an encapsulating agent.

3. The method of claim 2 wherein the active agent and encapsulating agent are also mixed with a solvent and the resulting mixture is spray dried prior to being added to the chewing gum.

4. The method of claim 3 wherein the encapsulating agent is selected from the group consisting of maltodextrin and gum arabic.

5. The method of claim 2 wherein the active agent is fluid-bed coated with a solution of encapsulating agent and solvent in order to increase the rate of release of the active agent in the chewing gum.

6. The method of claim 2 wherein the active agent is encapsulated by coacervation in order to decrease the rate of release of active agent in chewing gum.

7. The method of claim 2 wherein the active agent is mixed with a molten encapsulating agent and the active agent is encapsulated by spray chilling in order to decrease the rate of release of the active agent in the chewing gum.

8. The method of claim 2 wherein the active agent is mixed with a polymer as the encapsulating agent and the resulting mixture is extruded into fibers in such a way as to encapsulate the active agent in order to decrease the rate of release of the active agent in the chewing gum.

9. The method of claim 8 wherein the polymer is selected from the group consisting of PVAC, hydroxypropyl cellulose, polyethylene and plastic polymers.

10. The method of claim 1 wherein the active agent is mixed with an absorbent as the modifying agent.

11. The method of claim 1 wherein another active agent is added to the chewing gum formulation.

12. The method of claim 11 wherein the other active agent has been treated to modify its release rate from the chewing gum.

13. A chewing gum product made according to the method of claim 1.

14. The method of claim 1 wherein the effective amount of active agent in the chewing gum formulation is from about 0.2% to about 5% in the chewing gum product.

15. A method of producing a chewing gum containing a physically-modified active agent in order to control the release rate of the active agent comprising the steps of:

a) mixing a quantity of the active agent, which comprises one or more materials selected from the group consisting of benzooin, glucosamine, grape seed extract,

quarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lecithin, lycopene, polyphenol, psyllium, chromium picolinate and phenylpropanolamine, with a high-potency sweetener selected from the group consisting of neotame, aspartame, alitame, salts of acesulfame, cyclamate and its salts, saccharin and its salts, thaumatin, monellin, dihydrochalcones, sucralose and combinations thereof, and an agglomerating agent and solvent to partially coat the active agent, agglomerating agent and high-potency sweetener;

b) removing the solvent from the mixture of active agent, high-potency sweetener and agglomerating agent to form a dried material; and

c) adding a quantity of the dried material to a chewing gum formulation to provide an effective amount of the active agent in the gum.

16. The method of claim 1 wherein the dried material is ground to a powder prior to adding the dried material to the chewing gum.

17. A chewing gum product made according to the method of claim 15.

18. The method of claim 15 wherein the effective amount of active agent in the chewing gum formulation is from about 0.2% to about 5% in the chewing gum product.

19. A method of producing a chewing gum product containing an active agent, which comprises one or more materials selected from the group consisting of benzoin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lycopene, polyphenol, psyllium, chromium picolinate and phenylpropanolamine, wherein the active agent is a part of a rolling compound applied on the chewing gum product.

20. A chewing gum product made according to the method of claim 19.

21. A method of producing a chewing gum product containing an active agent, which comprises one or more materials selected from the group consisting of benzoin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lycopene, polyphenol, psyllium, chromium picolinate and phenylpropanolamine, wherein the active agent is part of the liquid in a liquid-center chewing gum product.

22. A chewing gum product made according to the method of claim 21.

23. A method of producing a chewing gum product containing an absorption-enhanced active agent in order to control the absorption rate of the active agent comprising the steps of:

a) mixing a quantity of the active agent, which comprises one or more materials selected from the group consisting of nutraceuticals and nutritional supplements, with an absorption enhancing agent selected from the group consisting of ethanol, polyethylene glycol, 2-pyrrolidones, myristic acid, p-phenyl phenol, nitrobenzene, stearyl alcohol, cetyl alcohol, croton oil, liquid paraffin, dimethyl sulfoxide, non-ionic surfactants, liposomes, lecithin fractions, long chain amphipathic molecules and mixtures thereof; and

b) incorporating a quantity of the mixture into a chewing gum formulation to provide an active agent level in the chewing gum formulation of from about 12 micrograms to about 250 milligrams per gram of chewing gum product.

24. A chewing gum product made according to the method of claim 23.

25. A coated chewing gum product containing an active agent comprising a compound selected from the group consisting of capicum, chamomile, cat's claw, echinacea, garlic, ginger, green tea, golden seal, kava kava, nettle, passion flower, saw palmetto, St. John's wort, valerian, benzoin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lycopene, polyphenol, psyllium, chromium picolinate, phenylpropanolamine and mixtures thereof, wherein the active agent is a part of a coating on a chewing gum pellet.

26. A method of producing coated chewing gum products containing at least one active agent in the coating, the active agent comprising a compound selected from the group consisting of capicum, chamomile, cat's claw, echinacea, garlic, ginger, green tea, golden seal, kava kava, nettle, passion flower, saw palmetto, St. John's wort, valerian, benzoin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lycopene, polyphenol, psyllium, chromium picolinate, phenylpropanolamine and mixtures thereof, comprising the steps of:

a) providing chewing gum product cores;

b) providing a coating solution;

c) coating the chewing gum product cores with the coating solution to provide coated chewing gum products, the coating including the active agent at a level of from about 12 micrograms to about 250 milligrams per gram of coated chewing gum product.

27. The method of claim 26 wherein the active agent is mixed in the coating solution prior to coating the cores.

28. The method of claim 27 wherein the active agent is also mixed with a solvent before adding to the coating solution and the resulting mixture is added to the chewing gum coating.

29. The method of claim 28 wherein the solvent is water, alcohol or flavor.

30. The method in claim 26 wherein a high-potency sweetener selected from the group consisting of aspartame, alitame, salts of acesulfame, cyclamate and its salts, saccharine and its salts, neotame, thaumatin, monellin, dihydrochalcones, sucralose and combinations thereof is mixed in the coating solution.

31. The method of claim 26 wherein the coating operation includes the application of multiple coats of coating solution and application of powder material between coats of coating solution.

32. The method of claim 31 wherein the active agent is included in the powder material.

33. The method of claim 31 wherein an active agent is included in both the coating solution and the powder material.

34. The method of claim 26 wherein an active agent is also included in the chewing gum cores.

35. The method of claim 34 wherein the active agents in the gum cores and coating are the same.

36. The method of claim 34 wherein the active agent in the cores is different than the active agent in the coating.

37. The method of claim 34 wherein at least one of the active agents in the coating and in the cores is treated with a modifying agent to control the release of the active agent prior to being incorporated into the coating or into the cores.

38. The method of claim 26 wherein at least two different coating solutions are used to make the coating.

39. The method of claim 38 wherein the active agent is mixed with the first of the at least two different coating solutions and applied to the cores with the first coating

solution to form a film, and a second coating solution without an active agent is applied over the film coated cores.

40. The method of claim 26 wherein the active agent in the coating has been treated with a modifying agent to control its release prior to being used in the coating.

41. A method of producing coated chewing gum products containing at least one active agent in the coating the active agent comprising a compound selected from the group consisting of capsicum, chamomile, cat's claw, echinacea, garlic, ginger, green tea, golden seal, kava kava, nettle, passion flower, saw palmetto, St. John's wort, valerian, benzoin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lycopene, polyphenol, psyllium, chromium picolinate, phenylpropanolamine and mixtures thereof, comprising the steps of:

a) providing chewing gum product cores;

b) providing a coating solution;

c) coating the chewing gum product cores with the coating solution to provide coated chewing gum products, the coating including the active agent at a level of from about 0.2% to about 5% in the gum products.

42. A method of producing coated chewing gum products containing at least one active agent in the coating treated so as to modify the absorption of the active agent in the mouth,

the active agent comprising a compound selected from the group consisting of capsicum, chamomile, cat's claw, echinacea, garlic, ginger, ginko, ginseng, green tea, golden seal, kava kava, nettle, passion flower, saw palmetto, St. John's wort, valerian, benzoin, glucosamine, grapeseed extract, guarana, phosphatidylserine, phytosterols, phytochemicals, isoflavones, lecithin, lycopene, polyphenol, psyllium, chromium picolinate, phenylpropanolamine and mixtures thereof, comprising the steps of:

a) providing chewing gum product cores;

b) providing a coating solution;

c) coating the chewing gum product cores with the coating solution to provide coated chewing gum products, the coating including the active agent at a level of from about 12 micrograms to about 250 milligrams per gram of coated chewing gum product and an absorption enhancing agent selected from the group consisting of ethanol, polyethylene glycol, 2-pyrrolidones, myristic acid, p-phenyl phenol, nitrobenzene, stearyl alcohol, cetyl alcohol, croton oil, liquid paraffin, dimethyl sulfoxide, non-ionic surfactants, liposomes, lecithin fractions, and long chain amphipathic molecules and mixtures thereof.

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## United States Patent [19]

Vértesy et al.

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[45] Date of Patent: Jun. 20, 2000

[54] BISMUTH SALTS OF ANTIBIOTICS OF THE MOENOMYCIN GROUP, PROCESSES FOR THEIR PREPARATION, THEIR USE AND PHARMACEUTICALS COMPRISING SUCH SALTS

[75] Inventors: Laszló Vértesy, Eppstein; Michael Kurz, Hofheim; Astrid Markus, Liederbach; Gerhard Selbert, Darmstadt, all of Germany

[73] Assignee: Hoechst Aktiengesellschaft, Frankfurt am Main, Germany

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[58] Field of Search ..... 514/25, 53; 536/16.8, 536/17.2, 117, 53

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Primary Examiner—Elli Pescelev

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

## [57] ABSTRACT

The present invention relates to bismuth salts of antibiotics of the moenomycin group, processes for their preparation, their use and pharmaceuticals comprising such salts. The salts according to the invention contain antibiotics of the moenomycin group which are so-called phosphoglycolipid antibiotics and which are present individually or as a mixture, or derivatives thereof, and bismuth in defined stoichiometric ratios. They are outstandingly suitable, in particular, for controlling *Helicobacter pylori* and, thus, for example, for the therapy and prophylaxis of gastric disorders.

18 Claims, No Drawings



# BISMUTH SALTS OF ANTIBIOTICS OF THE MOENOMYCIN GROUP, PROCESSES FOR THEIR PREPARATION, THEIR USE AND PHARMACEUTICALS COMPRISING SUCH SALTS

The present invention relates to bismuth salts of antibiotics of the moenomycin group, processes for their preparation, their use and pharmaceuticals comprising such salts. The salts according to the invention contain antibiotics of the moenomycin group which are so-called phosphoglycolipid antibiotics and which are present individually or as a mixture, or derivatives thereof, and bismuth in defined stoichiometric ratios. They are outstandingly suitable, in particular, for controlling *Helicobacter pylori* and, thus, for example, for the therapy and prophylaxis of gastric disorders.

For the treatment and prevention of gastric ulcers or gastritis and also for the prophylaxis of stomach cancer, hitherto especially so-called antacids and, with particular success,  $H_2$  receptor blockers have been used. Meanwhile, it has been recognized that infections with the microorganism *Helicobacter pylori* are frequently responsible for gastric disorders such as, for example, gastric ulcers (see, for example, A. T. R. Axon, "Helicobacter pylori Infection", *J. Antimicrob. Chemother.* 32, Suppl. A, 61, 1993). The infection of the human stomach with the pathogenic gram-negative bacterium *Helicobacter pylori* causes temporary dyspeptic symptoms, but the microorganism has a high persistence. *H. pylori* is moreover the underlying pathogen in the chronically active type b gastritis and a significant risk factor for the occurrence of stomach cancer. The pathophysiological mechanisms by which *H. pylori* causes diseases of the stomach are still relatively unclear. It is known that the microorganism produces a number of potentially toxic enzymes and chemicals (urease, ammonia, vacuolizing cytotoxin). The persistence of the harmful bacterium and the lasting antigenic stimulus are probably causal for the destruction of the gastric mucous membrane which takes place long-term.

The therapeutic aim is the complete eradication of *H. pylori* in the stomach. The therapy of choice is at present a triple combination which consists of a so-called acid inhibitor, for example a proton pump inhibitor such as omeprazole, and two antibiotics, such as, for example, clarithromycin and amoxicillin. This triple therapy, however, is associated with disadvantages. As a result of differing diffusion properties, the three different substances, which should act together, do not uniformly reach the inflammatory foci caused by *H. pylori*. Thus, in order to achieve good healing results, very high doses, which are accompanied by serious side effects, are necessary. It is obvious that a triple therapy in other ways also generally has great disadvantages in comparison to the administration of two medicaments or even of only one medicament.

In EP-A-655 249, it has already been described that moenomycin antibiotics are also suitable as efficacious antibiotics for the control of *H. pylori* infections and thus for the treatment of gastric disorders such as, for example, gastric ulcers. The moenomycin antibiotics also display their action against *H. pylori* particularly advantageously on administration in combination with other antibiotics or other customary ulcer therapeutics or gastritis therapeutics, for example with antacids,  $H_2$  receptor blockers, proton pump inhibitors, muscarinic receptor blockers or, for example, also

with bismuth salts, such as, for example, bismuth nitrate, bismuth carbonate, bismuth salicylate or bismuth citrate.

The use of bismuth salts for the treatment of gastric ulcers has already been widely reported in the literature (see, for example, J. H. Walsh and W. L. Peterson, *New Eng. J. Med.* 333 (No. 15), 984-991, 1995). Bismuth compounds employed for this purpose are, in particular, basic bismuth compounds, inter alia, for example, bismuth subsalicylate, or also tripotassium dicitratobismuthate. The efficacy of the bismuth is, on the one hand, attributed to its astringent characteristics, on the other hand, however, direct effects of bismuth on *Helicobacter pylori* have also been described, such as, for example, the inhibition of the F1-ATPase from *H. pylori* (W. Beil and C. Birkholz, *Arch. Pharmacol.* 350, Suppl. R 1, 1994). The use of bismuth salts, in particular in the treatment of *Helicobacter pylori*-induced gastric ulcers, is therefore desirable.

Unfortunately, some disadvantages which are based on the chemical behavior of the bismuth salts stand in the way of the use of bismuth in the present form. Bismuth salts are very often poorly soluble in aqueous medium. So-called basic salts which contain the  $BiO^{3+}$  ion and which are also designated as bismuth subsalts are formed in aqueous medium from the  $Bi^{3+}$  ion. Basic bismuth salts of this type are deposited from aqueous solution, i.e. they form poorly soluble precipitates, and are thus not available or only limitedly available for biological action. The dissolved portions form colloids. As a result of these physicochemical properties, bismuth salts often have compositions which can only be stated approximately (see Römpps Chemie Lexikon (Römpp's Chemical Encyclopedia), 9th Edition, Georg Thieme Verlag, Stuttgart, N.Y., 1989, p. 439; DAB (Deutsches Arzneibuch (German Pharmacopeia)) 8, 526-530) and have a poor dosability, which makes the estimation of their effect additionally difficult.

The desired administration of bismuth salts in combination with, for example, acid inhibitors and antibiotics for the treatment of gastric disorders, such as ulcers and *H. pylori* infections, thus proves to be very problematic because of the solubility and pharmacodynamics of the bismuth salts, which differ from the acid inhibitors and antibiotics. There has therefore been no lack of attempts to simplify corresponding triple therapies to dual therapies or monotherapies. A large number of combinations of proton pump inhibitors, antibiotics and bismuth salts have been investigated without it in the end being possible, however, to excel the triple therapy. There is thus still a need for efficacious, simple-to-use and highly tolerable medicaments for the treatment of gastric disorders such as gastric ulcers or for the prophylaxis of stomach cancer.

Surprisingly, it has now been found that from the antibiotics of the moenomycin group and their derivatives, which are capable of salt formation at their acidic groups such as the phosphoric acid groups (or phosphoric ester groups) and/or the carboxylic acid groups, stable well-defined bismuth salts are obtainable which contain the antibiotic component present in the form of individual compounds or of mixtures and the bismuth in stoichiometric ratios. The action of these salts is clearly superior to the action of the pure antibiotics from the moenomycin group in the control of *Helicobacter pylori* or in the treatment and prophylaxis of gastric disorders, and they can be employed in the form of a dual therapy or even of a monotherapy. The discovery of well-defined bismuth salts of the antibiotics of

the moenomycin group of this type is all the more surprising, as the conventional processes for obtaining such salts, such as precipitation from aqueous solution, dialyses or ion-exchanger applications, fail because of the already-discussed low solubility of the starting bismuth salts. They also fail because of the neutralization of the free acids of the antibiotics of the moenomycin group by basic bismuth, for example bismuth hydroxide.

The present invention thus relates to bismuth salts of antibiotics of the moenomycin group which antibiotics are present individually or as a mixture, and of their derivatives, and physiologically tolerable salts thereof. The bismuth salts according to the invention are stoichiometric compounds, i.e. defined chemical compounds of salt-like character which contain the acidic antibiotic(s) or derivatives thereof present in the new salts in anionic form and the bismuth in specific stoichiometric ratios. They are bismuth(III) salts, but they are not basic bismuth salts and do not have the disadvantages thereof explained above.

The stoichiometric ratio in which the bismuth and the antibiotic(s) or its/their derivatives are present in the salts according to the invention depends, for example, on the number of the acidic groups in the molecules of the antibiotic(s) and can be adjusted by means of the preparation conditions used, for example, by means of the molar ratio of the starting compounds employed in the preparation. A characteristic structural unit in antibiotics of the moenomycin group is the phosphoglyceric acid group or, as a part thereof, the doubly esterified phosphoric acid group, at whose free acid function salt formation can take place and which then represents a bismuth binding site. The stoichiometric ratio in the salts according to the invention can be indicated, for example, by indicating the number of moles or number of atoms of bismuth which is present per mole of the antibiotic(s), or it can also be indicated in a simple manner, for example, by indicating the phosphorus/bismuth molar ratio or atomic ratio, which is easy to determine. This ratio can be, for example, 1:1 or 1:2 (in the latter case this means that one bismuth atom is present per two phosphorus atoms or phosphoric acid groups in a salt according to the invention). The ratio, however, can also assume other values, also nonintegral values, for example if the salt according to the invention is derived from a mixture of two or more different antibiotics. If such a ratio, for example the ratio 1:1, is specified for the characterization of a salt according to the invention, then, of course, in macroscopic samples, such as are obtained, for example, in the industrial production of the salts according to the invention, the experimentally determined value can vary and differ slightly from the desired ideal value (for example 1:1), for example as a result of varying ratios of antibiotics or of by-components contained, and the indication of such a stoichiometric ratio for a substance according to the invention thus also includes, of course, ratios differing insignificantly therefrom.

Numerous antibiotics of the moenomycin group or their derivatives contain, in addition to the phosphoric acid group mentioned, one or, for example in the case of the derivatives, optionally also several carboxylic acid groups, at which salt formation with the bismuth can likewise take place. If the antibiotics, for example, contain a total of two acid functions in the molecule, such as, for example, the frequently occurring representatives having an acidic HO group in the phosphoric acid unit and having a COOH group, then they can bind two equivalents of bismuth or enter into two (salt)

bonds with the bismuth. The third valency of the trivalent bismuth can then be saturated, for example, by a (salt) bond to additional anions (or anion equivalents), which are then contained in the salts according to the invention in addition to the antibiotics and the bismuth and which can originate, for example, from the starting bismuth salt used in the preparation of the salts according to the invention. The third valency of the bismuth, however, can also be saturated by a (salt) bond to a phosphoric acid group or carboxylic acid group in a second molecule of the antibiotic whereby finally a salt according to the invention results which contains two bismuth atoms per three molecules of the designated antibiotics or per three phosphorus atoms. Accordingly, also in other antibiotics and very generally in the compounds according to the invention valencies of the bismuth can be saturated by additional anions. Suitable additional anions of this type are, in particular, physiologically tolerable anions, for example chloride, bromide, nitrate, sulfate, phosphate, and other inorganic and organic anions which can be employed in pharmaceuticals, such as acetate, benzoate, citrate, tartrate, methanesulfonate, etc. In the salts according to the invention there can also be present more than one such additional anions in the form of a mixture.

Preferred bismuth salts according to the invention are those which, on account of their stoichiometric ratio bismuth: antibiotic, contain an additional physiologically tolerable anion for the neutralization of the bismuth, in particular one of the abovementioned anions. These salts can be regarded as a cationic complex of the bismuth and the antibiotic(s), for which the physiologically tolerable anion represents the negative counter ion. Bismuth salts according to the invention are particularly preferred in which the bismuth and the antibiotic present individually or as a mixture (or the bismuth and the phosphorus in the partially esterified phosphoric acid groups) are present in a molar ratio or atomic ratio of 1:1 (or approximately 1:1) and which contain an additional physiologically tolerable anion, it being possible for this anion to be a singly charged anion or an equivalent of a multiply charged anion. These particularly preferred salts can be represented by the formula  $(A Bi)^+ X^-$ , in which A is an antibiotic of the moenomycin group or a derivative thereof present individually or as a mixture, which contains two acidic groups present in anionic form, and  $X^-$  is a physiologically tolerable singly charged anion or an equivalent of a physiologically tolerable multiply charged anion.

The antibiotics of the moenomycin group are phosphoglycolipid antibiotics. Instead of the term antibiotics of the moenomycin group used here, in some cases the term phosphoglycolipid antibiotics is also used for these compounds. The present invention includes the bismuth salts of all antibiotics of this group. In particular, antibiotics of the moenomycin group are to be understood as meaning the actual moenomycins, i.e. moenomycin itself, and, for example, prasinomycin (obtainable from *Streptomyces prasinsus*), diumycin (macarbomycin, obtainable from *S. umbrinus* or *S. phaeochromogenes*), 11837 R.P. (obtainable from *S. viridans*), 8036 R.P. (quebemycin, obtainable from *S. canadiensis*), 19402 R.P. (obtainable from *S. peruviansis*), ensachomycin (obtainable from *S. cinnamonensis*), prenomycin (obtainable from *S. ambofaciens*), teichomycin (obtainable from *Actinoplanes teichomyceticus*), pholipomycin (obtainable from *S. livido clavatus*) and others, which are all related phosphorus-containing acidic glycolipids. The

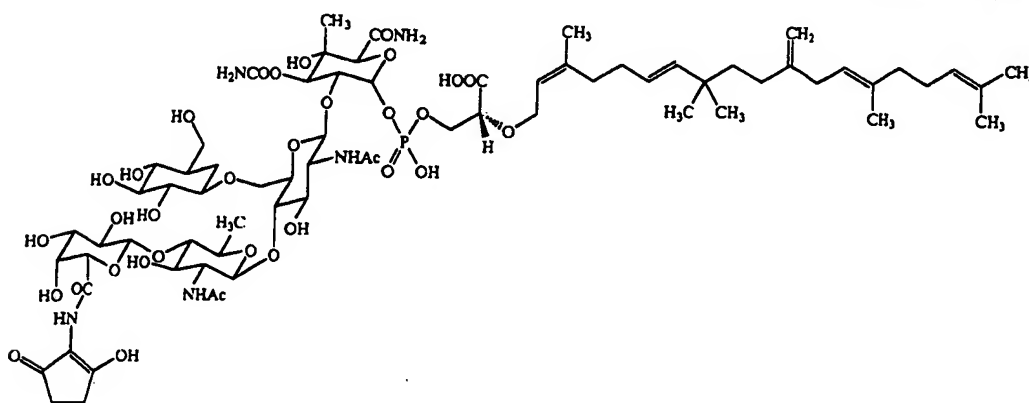
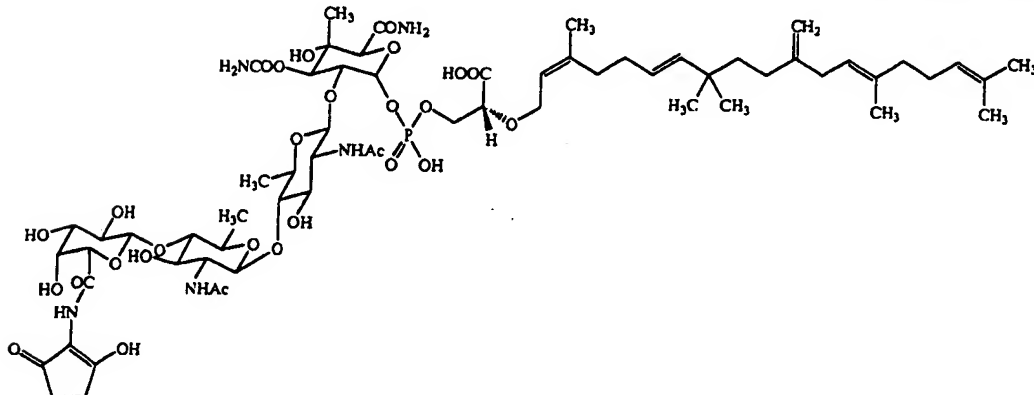
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bismuth salts of moenomycin itself are preferred. The individual antibiotics of the moenomycin group, again, are often complexes of several, structurally differing individual components. Individual components of moenomycin itself which may be mentioned, for example, are the moenomycins A,  $A_{1,1}$ ,  $A_{1,2}$ ,  $B_1$ ,  $B_2$ ,  $C_1$ ,  $C_2$ ,  $C_3$ ,  $C_4$  and others, in some cases differing notations being common, for example  $A_{1,2}$ . These individual components are obtainable from *Streptomyces bambergensis*, *S. ghanaensis*, *S. edersensis*, *S. geysirensis*, *S. prasinus*, or *S. livido clavatus*. Preferred individual components of moenomycin itself with respect to the present invention are moenomycin A (formula I) and moenomycin

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$C_3$  (formula II) (in the formulae Ac is acetyl). A particularly preferred individual component is moenomycin A. With respect to further details of the antibiotics of the moenomycin group and especially moenomycin itself and its individual components and also other structural formulae, reference is made to the literature, for example to the article by G. Huber in "Antibiotics", ed. F. Hahn, Springer-Verlag, Berlin 1979, Vol. V, Part 1, pages 135-153, or to EP-A-655 249, which corresponds to U.S. patent application Ser. No. 08/348,815, which inasmuch are completely part of the present disclosure and are incorporated herein by reference.

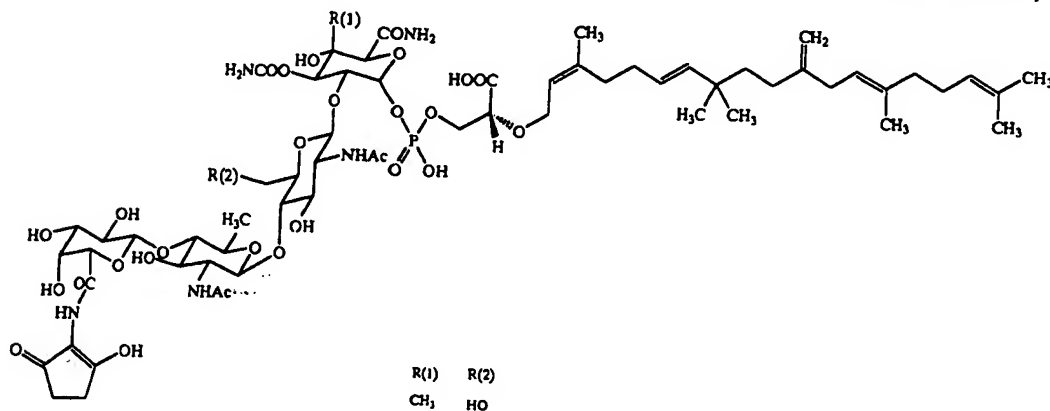
Formula I (moenomycin A)

Formula II (moenomycin  $C_3$ )

Other components of moenomycin itself which form part of the present invention are represented, for example, by moenomycin C<sub>1</sub> (M. Heßler-Klitz et al., *Tetrahedron*, Vol. 49, No. 35, pp. 7667-7678, 1993, hereby incorporated by reference) and moenomycin C<sub>4</sub> (formula III).

or more individual antibiotics or starting mixtures, for example to obtain a specific profile of action.

The present invention also relates to the physiologically tolerable salts of the bismuth salts of the antibiotics of the moenomycin group. As salts there can already be regarded

Formula III (moenomycin C<sub>4</sub>)

Derivatives of antibiotics of the moenomycin group are to be understood as meaning, for example, structurally modified antibiotics which are suitable for the salt formation to be carried out according to the present invention and which are obtainable, for example, by chemical, biochemical or microbial conversion of functional groups, for example by hydrolyses, acylations or alkylations, but likewise, for example, also suitable degradation products of the antibiotics. The bismuth salts of the actual antibiotics of the moenomycin group are preferred, i.e. compounds in which no additional derivatization has been performed.

The antibiotics of the moenomycin group and likewise the actual moenomycins are in general obtained by fermentation of microorganisms and subsequent purification. Microorganisms employed are, for example, *Streptomyces bambergensis*, *S. ghanaensis*, *S. edersensis*, *S. geysirensis*, *S. prasinus*, *S. lividoclavatus*, and others (G. Huber in "Antibiotics", ed. F. Hahn). In this case, the antibiotics are often obtained as mixtures or as complexes of individual components which may have varying compositions, and they are often also used in the form of such mixtures. If desired, the mixtures can be separated by customary methods into the pure or largely pure individual antibiotics or individual components, which have defined activities and are administered preferably. Correspondingly, the bismuth salt according to the invention can also be derived from mixtures of antibiotics of the moenomycin group or from individual antibiotics or from individual components of the complexes. The bismuth salts of all individual antibiotics of the moenomycin group and all possible combinations of more than one antibiotics of the moenomycin group are covered by the present invention. The mixtures can be derived from two or more individual antibiotics, it being possible for these to be individual components of a specific antibiotic, for example of moenomycin itself, and/or for these to belong to different antibiotics of the moenomycin group. Mixtures of antibiotics contained in the salts according to the invention can have the composition in which they are obtained during their synthesis or purification or they can, for example, also be prepared by specific mixing of two

the compounds according to the invention illustrated above which contain additional anions such as chloride, bromide, nitrate etc. If a bismuth salt according to the invention contains, as an additional anion, an anion of a polybasic acid, for example sulfuric acid or citric acid, it is also possible for only one of these acid functions to be neutralized by bismuth and the second or others to be completely or partially present, for example, as metal salts or ammonium salts. Acidic groups which are present in the molecule of the antibiotic or which are produced by derivatization, which are not neutralized by salt formation with the bismuth, can also be present as metal salts or ammonium salts, or basic groups present in the antibiotics or produced by derivatization, for example by hydrolysis of amide groups to amino groups, can be present as acid addition salts. Suitable metal salts are, in particular, alkali metal salts and alkaline earth metal salts, for example sodium, potassium, calcium or magnesium salts. Ammonium salts can be derived from ammonia and from organic amines. Acid addition salts can be derived, for example, from hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid or other inorganic and organic acids which can be employed in pharmaceuticals, such as acetic acid, benzoic acid, citric acid, tartaric acid, methanesulfonic acid and others. The salts can be prepared by the customary processes known to the person skilled in the art. Internal salts (betaines) are also covered by the invention. The present invention furthermore relates to solvates of the bismuth salts of antibiotics of the moenomycin group, for example with water or alcohols, and other derivatives, for example esters, and active metabolites of the compounds according to the invention.

The bismuth salts of the antibiotics of the moenomycin group according to the invention are obtainable, for example, by reacting the antibiotic(s) of the moenomycin group or in particular its/their customarily used salts with a bismuth salt in a solvent or dispersant. This preparation process also is a subject of the present invention. The antibiotics in this case are customarily employed in the form of alkali metal salts or ammonium salts, preferably in the form of the sodium, potassium or ammonium salts, which

are adequately soluble in organic solvents. Solvents used for the reaction are preferably organic solvents, however organic solvents containing water can also be used. Preferably, the antibiotics (or their starting salts) and the starting bismuth salt are employed in the form of solutions, particularly preferably, especially the starting bismuth salt is employed in the form of a solution in an organic solvent. In the reaction, defined bismuth salts of stoichiometric composition of the antibiotics of the moenomycin group are formed, which are often poorly soluble in organic solvents and are already deposited from the reaction mixture in largely pure form, and which can be separated off in a simple manner or which otherwise can be isolated according to customary methods and, if desired, further purified.

The composition of the products according to the invention thus obtainable and the proof that they are not physical mixtures of bismuth compounds with the antibiotics, but homogeneous chemical compounds of stoichiometric composition which contain the bismuth, the antibiotics and optionally, for example, an additional anion can be determined by the customary analytical processes known to the person skilled in the art. The content of bismuth and other elements can be determined in a known manner, for example by elemental analysis. The antibiotic content of a salt according to the invention can be demonstrated and identified, for example, by recording NMR spectra.

NMR spectroscopy also allows an unequivocal conclusion that defined bismuth salt formation takes place on certain acidic groups of the antibiotic. For example, a comparison of the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR signals of a bismuth salt according to the invention with that of the corresponding sodium salt of the antibiotic used as a starting material for its synthesis shows that specific signals are shifted in a characteristic manner, in particular those of atoms which are adjacent to the acidic centers at which the bismuth salt formation takes place (cf. NMR data in Example 1). This proves that the substances according to the invention are novel, well-defined compounds and confirms their structure.

X-ray spectrometric processes such as X-ray fluorescence analysis and moreover scanning transmission electron microscopy, which can be coupled with energy-dispersive X-ray microanalyses, are also highly suitable. Beside the detection of the elements, for example of the bismuth or of the phosphorus, these analytical methods allow the determination of the ratio of the elements present in different, extremely small sample sites, such as, for example, the ratio of bismuth to phosphorus, or, for example, to chlorine, sodium and other elements. The products according to the invention are also homogeneous according to energy-dispersive X-ray microanalysis, the concentration ratio of, for example, bismuth to phosphorus is always constant, a compound of stoichiometric composition is thus present.

As already stated, preferred solvents in the preparation of the bismuth salts according to the invention are organic solvents. However, aqueous-organic solvents can also be employed in which the water content should be so low that substantially no hydrolysis of the bismuth salt employed as a starting material occurs under the reaction conditions. The permissible water content depends on the individual case. Suitable organic solvents are, for example, lower alcohols, in particular methanol and ethanol, ethylene glycol monomethyl ether, glycols, such as, for example, ethylene glycol or 1,2-propylene glycol, dimethyl sulfoxide (DMSO), dimethylformamide, ethers such as dioxane, tetrahydrofuran, ethylene glycol ethers, and mixtures of these solvents and other solvents. In particular, lower alcohols are preferred in which the antibiotics of the moenomycin group or their salts dissolve well, such as methanol or ethanol.

For the preparation of the compounds according to the invention, the antibiotics of the moenomycin group are preferably initially introduced as a solution, for example in methanol, having a concentration from, customarily, 0.1 to 10% by weight, preferably from 1 to 5% by weight. As already stated, the antibiotics can be employed in the bismuth salt formation in the form of mixtures of several antibiotics or in the form of complexes of one antibiotic, for example of moenomycin, or as individual components, for example as moenomycin A or  $\text{C}_3$ , where, as also already stated, salts such as, for example, the sodium salts or ammonium salts are customarily employed. Suitable bismuth(III) salts are in particular salts of the  $\text{Bi}^{3+}$  ion, which dissolve well in organic solvents, such as, for example, bismuth chloride ( $\text{BiCl}_3$ ), bismuth nitrate ( $\text{Bi}(\text{NO}_3)_3$ ), bismuth bromide ( $\text{BiBr}_3$ ) and others. The employed solution of bismuth(III) salt in an organic solvent customarily has a concentration from 0.01 to 1 mol per liter, preferably from 0.1 to 0.5 mol per liter. The bismuth solution is preferably metered into the solution of the antibiotic, and while doing this often, but of course depending on the individual case, the salt according to the invention is already deposited. The molar ratio of the reactants can be varied within a wide range. Preferably, equimolar ratios are used, in particular if the preferred bismuth salts are to be prepared which contain the antibiotic (or the phosphorus) and the bismuth in the molar ratio or atomic ratio 1:1. As already stated, various bismuth salts can be obtained depending on the preparation conditions used.

In general, the reaction of the bismuth salts with the antibiotics is carried out in the temperature range from  $-20^\circ\text{C}$ . to  $80^\circ\text{C}$ ., preferably in the range from  $10^\circ\text{C}$ . to  $30^\circ\text{C}$ . The reaction is advantageously carried out by slowly metering in in the course of, in general, 20 minutes to 2 hours. In a more rapid procedure, if the product is deposited, so-called inclusions can adversely affect the purity of the product. If the product is poorly soluble in the solvent employed, then, for isolation of the product, the precipitate formed in the deposition can be separated off by centrifuging or filtering and, if desired, purified, for example by suspending in a suitable organic solvent and centrifuging or filtering again. If the product is readily soluble, such that it remains in solution, completely or to a relatively large extent, then according to the customary procedures the solvent can initially be partially or completely removed, for example by vacuum distillation and/or freeze drying, and/or a solvent can be added in which the product is poorly soluble, and the product deposited can then be separated off. For isolation, however, chromatographic processes can also be employed. After drying, the product is obtained as a white or pale powder, which in general is highly soluble in water and soluble in DMSO, but poorly soluble in many other organic solvents. If desired, the product can additionally be purified by customary processes, for example by reprecipitation or chromatography.

Furthermore, bismuth salts according to the invention which contain an additional anion can in particular be obtained, for example, by ion-exchange processes. Thus, for example, a bismuth salt according to the invention which contains a specific anion can be converted by anion exchange according to customary procedures, for example by reaction with a salt or an acid in a solvent or by chromatography, into another bismuth salt according to the invention which contains another physiologically tolerable anion as an additional anion.

The biological and therapeutic actions of the antibiotics of the moenomycin group, in particular of the moenomycins

themselves, and the advantages of the use of these antibiotics in the therapy and prophylaxis of gastric disorders are described in detail in EP-A-655 249. The bismuth salts according to the invention actually even excel the advantageous antibacterial and healing-promoting properties of the moenomycins to a considerable extent. This is seen both in in vitro experiments and in vivo. As detailed further below, the action of the bismuth salt of moenomycin A, for example, is clearly superior to the action of moenomycin A (as a sodium salt) already in in vitro experiments. The moenomycin and the bismuth act synergistically. In the form of the salts according to the invention, both components can reach the inflammatory focus together by diffusion and display their actions there, which in the case of the customary administration of an antibiotic and of a separate bismuth salt is not possible or only possible to a very much smaller extent.

A crucial advantage of the compounds according to the invention is that, because of the higher activity of the compounds according to the invention, smaller doses can be administered in order to achieve the therapeutic aim, for example the eradication of *H. pylori*, and that fewer side effects are associated therewith. The wide and high efficacy of the bismuth salts according to the invention allows their use alone as an antimicrobial agent instead of two antibiotics in conventional therapy. Triple therapy can thereby be simplified to dual therapy, in which beside the bismuth salt according to the invention, for example, only an antacid (for example omeprazole, lansoprazole, pantoprazole or others) is administered. As a result, the patient is treated more gently and costs are lowered. The eradication of *H. pylori* is even possible using the bismuth salts according to the invention on its own without any additional medication. This monotherapy is far superior to other ulcer therapies with respect to simplicity, tolerability and cost effectiveness.

The bismuth salts of antibiotics of the moenomycin group according to the invention and their physiologically tolerable salts can thus be used in animals, preferably in mammals, and in particular in man, as pharmaceuticals per se, in mixtures with one another or in the form of pharmaceutical preparations. The present invention also relates to the bismuth salts according to the invention and their physiologically tolerable salts for use as pharmaceuticals, to their use in the therapy and prophylaxis of ulcers generally, such as, for example, duodenal ulcer or peptic ulcer, of gastric disorders, in particular gastric ulcers or gastritis, in the prophylaxis of stomach cancer, and generally in the control of *Helicobacter pylori*, and to their use for the production of medicaments for the uses mentioned. The present invention furthermore relates to pharmaceutical preparations which, as active constituent, contain an efficacious dose of at least one bismuth salt according to the invention and/or a physiologically tolerable salt thereof in addition to customary, pharmaceutically innocuous excipients and/or auxiliaries. The pharmaceutical preparations normally contain 0.5 to 95 percent by weight of the bismuth salts according to the invention and/or their physiologically tolerable salts. The pharmaceutical preparations can be prepared in a manner known per se. For this purpose, the bismuth salts according to the invention and/or their physiologically tolerable salts are brought, together with one or more solid or liquid pharmaceutical excipients and/or auxiliaries and, if desired, in combination with other pharmaceutically active compounds, into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine. These pharmaceuticals are mainly intended for oral administration.

The bismuth salts according to the invention and their physiologically tolerable salts can also be combined with other pharmaceutically active compounds to achieve an advantageous therapeutic action, in particular with one or more further pharmaceutically active compounds for the treatment of gastric disorders or ulcers. For the therapeutic and prophylactic uses mentioned, suitable additional active compounds derive, for example, from the antacids group, such as, for example, sodium bicarbonate, aluminum hydroxide, magnesium hydroxide, magnesium trisilicate, aluminum magnesium silicate hydrate, aluminum sodium carbonate dihydroxide, magnesium carbonate, calcium carbonate or hydrotalcite. Other suitable additional active compounds derive from the  $H_2$  receptor blocker group, such as, for example, famotidine, nizatidine, roxatidine acetate, ranitidine or cimetidine. Other suitable additional active compounds are muscarinic receptor blockers such as propantheline bromide, pirenzepine, or other anti-ulcer agents such as omeprazole, lansoprazole, pantoprazole, misoprostol, or also additional bismuth salts such as bismuth nitrate, bismuth carbonate, bismuth salicylate or bismuth citrate. Other additional active compounds suitable for the therapy according to the invention belong to the antibiotics group, such as, for example, tetracycline, metronidazole, amoxycillin, nisin, clarithromycin, imipenem or amikacin. A preferred combination contains the bismuth salts according to the invention together with a proton pump inhibitor such as, for example, omeprazole, lansoprazole, pantoprazole or others. It may also be advantageous to combine the bismuth salts according to the invention with several of the abovementioned additional active compounds or with further active compounds for other indications. The administration of the components of the combinations mentioned can be carried out together or in separate form, and it can be carried out in a single administration or alternatively performed sequentially.

Suitable pharmaceutical administration forms for the administration of the bismuth salts according to the invention are, for example, capsules, for example hard or soft capsules, tablets, pastilles, lozenges, roll treatments (i.e. treatments in which the medicine taken is distributed in the stomach by the patient lying some minutes on the back, then some minutes on the side, then some minutes on the front, etc.), dispersible powders and granules, microbeads, solutions or suspensions, in particular aqueous solutions and suspensions, emulsions, syrups and elixirs, and similar forms known in the art. Solid administration forms are preferred, in particular those which release the active principle in the stomach.

The pharmaceutical preparations can be prepared by the appropriate methods known in the art for the production of pharmaceutical preparations using pharmaceutically acceptable, nontoxic auxiliaries and excipients. As excipients, tablets for oral administration can contain, for example, inert extenders (such as, for example, sodium chloride, lactose, calcium phosphate or sodium phosphate), granulating agents or disintegrants (for example potato starch, alginic acid), binders (such as, for example, starch, gelatin or gum arabic) and lubricants (such as, for example, magnesium stearate, stearic acid or talc). The tablets can be uncoated or they can be coated by means of the known techniques in order to delay dissolution and absorption in the stomach and thus to give a lasting action over a relatively long period of time. Thus, for example, a release-delaying substance such as, for example, glyceryl monostearate or glyceryl distearate can be employed. In hard gelatin capsules for oral administration, the active compound can be mixed, for example, with an inert solid extender, for example



calcium phosphate or kaolin, in soft gelatin capsules the active compound can be mixed, for example, with an aqueous medium, for example water, or an oily medium, for example peanut oil, liquid paraffin or olive oil. The excipients and/or auxiliaries suitable for the desired pharmaceutical formulation are familiar to the person skilled in the art on the basis of his expert knowledge. As auxiliaries there may be mentioned, for example, antioxidants, dispersants, emulsifiers, solubilizers, stabilizers, flavorings, sweeteners, colorants, preservatives, agents for achieving a depot effect, buffer substances, etc.

The dose to be administered of the bismuth salts according to the invention or of their physiologically tolerable salts depends on the individual case and is to be adapted to the conditions of the individual case for an optimum action as usual. Thus it depends, of course, on the frequency of administration and on the potency and duration of action of the compounds employed in each case for therapy or prophylaxis, but also on the nature and severity of the disease to be treated and on the sex, age, weight, state of health, nutrition, individual responsiveness of the human or animal to be treated, on interactions with other pharmaceuticals and on whether treatment is acute or prophylactic. Customarily, the daily dose in the case of oral administration of a pharmaceutical preparation to a human weighing approximately 75 kg is 5 mg to 5 g per person per day, preferably 50 mg to 2 g per person per day. The dose can be administered in the form of an individual dose or subdivided into several, for example, two, three or four, individual doses.

Apart from as pharmaceutically active compounds, the bismuth salts according to the invention can also be used, as already mentioned above, as intermediates for the production of other pharmaceutically active compounds. They can furthermore be employed as auxiliaries in biochemical or microbiological investigations or in diagnostic procedures, for example in *in vitro* diagnoses.

## EXAMPLES

### Example 1

Bismuth salt of moenomycin A in the chloride form (Formula:  $(C_{69}H_{106}BiN_5O_{34}P)^+$ , counterion:  $Cl^-$ ; MW 1825)

50 g of moenomycin A sodium salt were dissolved in 2 L of methanol and treated with stirring with 9.6 g of  $BiCl_3$  in 100 ml of methanol for 2 hours at room temperature. After gentle stirring for a further 15 minutes, the resulting white precipitate was washed several times with 2 L of methanol each by stirring the precipitate with a glass rod and collecting the undissolved bismuth salt of moenomycin A by centrifuging. After drying *in vacuo*, 28 g of product were obtained which after grinding and sieving was employed for the biological investigations. The product obtained was characterized, *inter alia*, by the following analyses.

a)  $^1H$ - and  $^{13}C$ -NMR

Chemical shifts (in ppm) of the moenomycin A bismuth salt in the chloride form obtained according to Example 1 and of the moenomycin A sodium salt as a comparison are shown (in  $d_6$ DMSO)

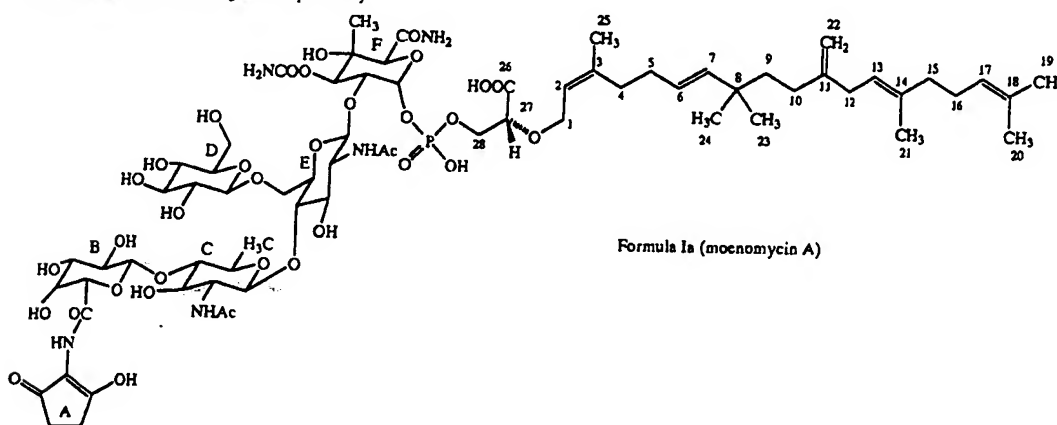
| Molecule position (see Formula Ia below) | Bi salt, chloride form<br>$^1H$ | Na salt<br>$^1H$ | Bi salt, chloride form<br>$^{13}C$ | Na salt<br>$^{13}C$ |
|--|---------------------------------|------------------|------------------------------------|---------------------|
| 1  | 4.07/3.94                       | 4.07/3.83        | 65.42                              | 64.78               |
| 2  | 5.33                            | 5.32             | 121.66                             | 123.51              |
| 3  | —                               | —                | 138.73                             | 136.84              |
| 4  | 2.06                            | 2.03             | 31.80                              | 31.96               |
| 5  | 2.05                            | 2.02             | 30.70                              | 30.88               |
| 6  | 5.25                            | 5.24             | 125.23                             | 125.43              |
| 7  | 5.36                            | 5.35             | 139.80                             | 139.79              |
| 8  | —                               | —                | 35.07                              | 35.19               |
| 9  | 1.33                            | 1.33             | 40.86                              | 40.91               |
| 10                                       | 1.86                            | 1.85             | 30.61                              | 30.68               |
| 11                                       | —                               | —                | 149.15                             | 149.21              |
| 12                                       | 2.66                            | 2.65             | 34.39                              | 34.47               |
| 13                                       | 5.12                            | 5.11             | 121.66                             | 121.75              |
| 14                                       | —                               | —                | 135.69                             | 135.81              |
| 15                                       | 1.98                            | 1.98             | 39.08                              | 39.22               |
| 16                                       | 2.05                            | 2.05             | 26.01                              | 26.08               |
| 17                                       | 5.07                            | 5.06             | 123.96                             | 124.05              |
| 18                                       | —                               | —                | 130.56                             | 130.70              |
| 19                                       | 1.63                            | 1.63             | 25.34                              | 25.48               |
| 20                                       | 1.55                            | 1.55             | 17.37                              | 17.53               |
| 21                                       | 1.57                            | 1.57             | 15.62                              | 15.71               |
| 22                                       | 4.66                            | 4.65             | 108.58                             | 108.70              |
| 23                                       | 0.94                            | 0.93             | 27.02                              | 27.11               |
| 24                                       | 0.94                            | 0.93             | 27.02                              | 27.11               |
| 25                                       | 1.70                            | 1.67             | 23.20                              | 23.28               |
| 26                                       | —                               | —                | *)                                 | 173.68              |
| 27                                       | 4.03                            | 3.64             | 77.69                              | 80.89               |
| 28                                       | 3.85                            | 3.99/3.75        | 65.23                              | 67.25               |
| A-NH                                     | 8.66                            | 7.47             | —                                  | —                   |
| A1                                       | —                               | —                | broad                              | 193.37              |
| A2                                       | —                               | —                | *)                                 | 109.67              |
| A3                                       | —                               | —                | broad                              | 193.37              |
| A4                                       | broad                           | 2.00             | *)                                 | 30.88               |
| A5                                       | broad                           | 2.00             | *)                                 | 30.88               |
| B1'                                      | 4.41                            | 4.33             | 102.87                             | 103.24              |
| B2'                                      | 3.41                            | 3.38             | 69.79                              | 70.24               |
| B3'                                      | 3.41                            | 3.37             | 72.48                              | 72.98               |



-continued

| Molecule position (see Formula Ia below) | Bi salt, chloride form<br><sup>1</sup> H | Na salt<br><sup>1</sup> H | Bi salt, chloride form<br><sup>13</sup> C | Na salt<br><sup>13</sup> C |
|--|--|---------------------------|---|----------------------------|
| B4'                                      | 3.93                                     | 3.92                      | 69.08                                     | 69.46                      |
| B5'                                      | 4.26                                     | 3.94                      | 74.31                                     | 75.36                      |
| B5'-C                                    | —  | —                         | 169.37                                    | 167.03                     |
| C1'                                      | 4.51                                     | 4.66                      | 101.09                                    | 100.98                     |
| C2'                                      | 3.52                                     | 3.52                      | 55.50                                     | 55.63                      |
| C2'-NH                                   | 7.81                                     | 8.08                      | —   | —                          |
| C2'-C                                    | —  | —                         | 169.44                                    | 170.03                     |
| C2'-Ac                                   | 1.88                                     | 1.90                      | 22.94                                     | 22.97                      |
| C3'                                      | 3.54                                     | 3.48                      | 71.66                                     | 72.89                      |
| C4'                                      | 3.21                                     | 3.15                      | 83.71                                     | 84.02                      |
| C5'                                      | 3.52                                     | 3.48                      | 70.32                                     | 70.73                      |
| C5'-Me                                   | 1.33                                     | 1.31                      | 17.37                                     | 17.53                      |
| D1'                                      | 4.35                                     | 4.37                      | 102.64                                    | 102.88                     |
| D2'                                      | 2.97                                     | 2.96                      | 73.41                                     | 73.49                      |
| D3'                                      | 3.25                                     | 3.26                      | 76.67                                     | 76.69                      |
| D4'                                      | 3.04                                     | 3.01                      | 70.33                                     | 70.24                      |
| D5'                                      | 3.21                                     | 3.21                      | 76.67                                     | 77.21                      |
| D6'                                      | 3.70/3.44                                | 3.71/3.44                 | 61.24                                     | 61.52                      |
| E1'                                      | 4.51                                     | 4.46                      | 101.09                                    | 101.53                     |
| E2'                                      | 3.37                                     | 3.55                      | 55.02                                     | 55.01                      |
| E2'-NH                                   | 7.41                                     | 7.61                      | —   | —                          |
| E2'-C                                    | —  | —                         | 169.03                                    | 169.81                     |
| E2'-Ac                                   | 1.82                                     | 1.82                      | 23.10                                     | 23.03                      |
| E3'                                      | 3.59                                     | 3.53                      | 71.83                                     | 72.79                      |
| E4'                                      | 3.35                                     | 3.35                      | 80.27                                     | 79.67                      |
| E5'                                      | 3.41                                     | 3.38                      | 73.83                                     | 72.03                      |
| E6'                                      | 3.97/3.54                                | 3.99/3.44                 | 67.39                                     | 68.28                      |
| F1'                                      | 5.67                                     | 5.75                      | 93.60                                     | 93.69                      |
| F2'                                      | 3.43                                     | 3.38                      | 76.63                                     | 77.21                      |
| F3'                                      | 4.91                                     | 4.90                      | 73.85                                     | 74.15                      |
| F3'-NH <sub>2</sub>                      | 6.25                                     | 6.36                      | —   | —                          |
| F3'-C'                                   | —  | —                         | 156.15                                    | 156.53                     |
| F4'                                      | —  | —                         | 72.60                                     | 72.53                      |
| F4'-Me                                   | 1.10                                     | 1.06                      | 16.21                                     | 16.04                      |
| F5'                                      | 4.21                                     | 4.28                      | 71.61                                     | 71.71                      |
| F5'-NH <sub>2</sub>                      | 7.42/7.02                                | 7.49/7.29                 | —   | —                          |
| F5'-C'                                   | —  | —                         | 171.79                                    | 171.80                     |

\*)These signals cannot be assigned unequivocally.



Formula Ia (moenomycin A)

## b) Electron-dispersive X-ray Microanalysis (EDX)

Ten powder agglomerates were investigated by means of EDX. The diameter of the sample sites investigated was in each case about 50 nm. Bismuth was detected at each site. The atomic ratio bismuth: phosphorus was always 1:1, i.e. the bismuth is homogeneously and stoichiometrically incorporated into the organic powder particles. Beside the bismuth and phosphorus (and also chlorine, carbon and oxygen), small amounts of sodium were detected in locally differing concentrations.

The supernatant from the moenomycin A/bismuth chloride precipitation was treated with 100 ml of DMSO, con-

centrated in vacuo to 200 ml and applied to a column packed with 20 L of Fractogel TSK HW-40. It was fractionally eluted using DMSO/methanol (1:1). The eluate fractions containing the bismuth salt of moenomycin A were combined and freed from the solvent by vacuum distillation and by freeze-drying. They afforded a further 21 g of the bismuth salt of moenomycin A in the chloride form, which was identical to the product first obtained.

## Example 2

Bismuth salt of moenomycin A in the nitrate form (Formula:  $(C_{69}H_{106}BiN_5O_{34}P)^+$ , counterion:  $NO_3^-$ ; MW 1851.5)

163 mg of moenomycin A sodium salt were dissolved in 4 ml of methanol and treated with stirring with a solution of 48.5 mg of bismuth(III) nitrate pentahydrate in 200  $\mu$ l of DMSO. A precipitate resulted, which was purified by suspending three times in methanol, centrifuging and separating off the supernatant. After drying the precipitate in vacuo, 112 mg of bismuth salt of moenomycin A in the nitrate form were obtained. Electron-dispersive X-ray microanalysis was carried out as in Example 1 and gave corresponding results, but no chlorine content.

According to the above Examples, the following bismuth salts of moenomycin antibiotics can also be obtained:

Moenomycin A<sub>3</sub> bismuth salt in the chloride form (Formula:  $(C_{68}H_{104}BiN_5O_{34}P)^+$ , counterion:  $Cl^-$ ; MW 1811)

Moenomycin C<sub>1</sub> bismuth salt in the chloride form (Formula:  $(C_{62}H_{94}BiN_5O_{28}P)^+$ , counterion:  $Cl^-$ ; MW 1632.8)

Moenomycin C<sub>3</sub> bismuth salt in the chloride form (Formula:  $(C_{63}H_{96}BiN_5O_{28}P)^+$ , counterion:  $Cl^-$ ; MW 1646.9)

Moenomycin C<sub>4</sub> bismuth salt in the chloride form (Formula:  $(C_{63}H_{96}BiN_5O_{29}P)^+$ , counterion:  $Cl^-$ ; MW 1662.9)

#### Biological Investigations

Antibacterial activity of the bismuth salts of antibiotics of the moenomycin group against *Helicobacter pylori* was assayed. *Helicobacter pylori* was precultured at 35° C. on tryptic soy-agar (+5% defibrinated sheeps' blood, +actidione 500  $\mu$ g/ml) under microaerophilic conditions (Anaerocult, Merck) in a CO<sub>2</sub> atmosphere (8–10% CO<sub>2</sub>) for 5 days. For the actual experiment, the grown cultures were removed completely from the preculture plate using a cotton swab, suspended in 0.9% strength NaCl solution and adjusted using McFarland standard to a microorganism density of  $3 \times 10^8$  cfu/ml. The in vitro activity of the test substances was determined by the agar dilution method using Columbia agar (+5% defibrinated sheeps' blood, +actidione, 500  $\mu$ g/ml) as test medium. The agar plates, which contained various concentrations of test substance (0.002 to 128  $\mu$ g/ml), were inoculated in a punctiform manner (multipoint inoculator, Denley) with the adjusted microorganism suspensions. Incubation was carried out under microaerophilic conditions (see above). After 5 days at 35° C., the lowest substance concentration was determined at which colony formation was not detectable visually, and defined as the minimum inhibitory concentration (MIC). Like the bismuth salts, the corresponding sodium salts were investigated for comparison.

Results: Minimum inhibitory concentration ( $\mu$ g/ml)

| Microorganism         | Moenomycin A sodium salt (Comparison) | Moenomycin A bismuth salt, chloride form (Example 1) |
|-----------------------|---------------------------------------|--|
| <i>H. pylori</i> P 42 | 2                                     | 0.5  |

What is claimed is:

1. A composition of matter, comprising a bismuth salt of an antibiotic of the moenomycin group or a physiologically tolerable salt thereof, wherein said antibiotic of the moenomycin group is present individually, or as a mixture, or as a derivative thereof.

2. The composition of matter of claim 1, wherein the antibiotic is one or more of moenomycin, prasinomycin, diumycin, 11837 R.P., 8036 R.P., 19402 R.P., ensachomycin, prenomycin, teichomycin or pholipomycin.

3. The composition of matter of claim 1, wherein the bismuth salt is derived from at least one of the components of moenomycin.

4. The composition of matter of claim 3, wherein the antibiotic is at least one of moenomycin A or moenomycin C<sub>3</sub>.

5. The composition of matter of claim 1, wherein said bismuth salt of an antibiotic of the moenomycin group further comprises a physiologically tolerable anion.

6. The composition of matter of claim 4, wherein said bismuth salt of an antibiotic of the moenomycin group further comprises a physiologically tolerable anion.

7. The composition of matter of claim 1, wherein the bismuth and the antibiotic are present in a molar ratio of approximately 1:1.

8. A method of preparing the composition of matter of claim 1, comprising reacting at least one antibiotic of the moenomycin group or a salt thereof with a bismuth salt in a solvent or dispersant.

9. A pharmaceutical composition, comprising a bismuth salt of claim 1 or a physiologically tolerable thereof, and a pharmaceutically tolerable excipient.

10. A pharmaceutical composition of claim 9, further comprising an active compound for the treatment of gastric disorder or ulcers.

11. A method for treating ulcers, gastric disorders, gastric ulcers, or gastritis, comprising administering to a host in need thereof an effective amount of a bismuth salt of claim 1 or a physiologically tolerable salt thereof.

12. A pharmaceutical composition for the control of *Helicobacter pylori*, comprising an effective amount of at least one bismuth salt of claim 1 or of a physiologically tolerable salt thereof, together with a pharmaceutically tolerable excipient or auxiliary.

13. A method for controlling *Helicobacter pylori*, comprising administering to a host in need thereof an effective amount of a bismuth salt of claim 1 or a physiologically tolerable salt.

14. A pharmaceutical composition for the reduction of the risk of stomach cancer in which *H. pylori* is a causative factor, comprising an efficacious amount of at least one bismuth salt of claim 1 or of a physiologically tolerable salt thereof, together with a pharmaceutically tolerable excipient or auxiliary.

15. A method for reducing the risk of stomach cancer in which *H. pylori* is a causative factor, comprising administering to a host in need thereof an effective amount of a bismuth salt of claim 1 or a physiologically tolerable salt thereof.

16. A pharmaceutical composition for treating ulcers, gastric disorders, gastric ulcers, or gastritis, comprising an effective amount of at least one bismuth salt of claim 1 or of a physiologically tolerable salt thereof, together with a pharmaceutically tolerable excipient or auxiliary.

17. A method for controlling conditions in which *H. pylori* is a causative factor, comprising administering an effective amount of a bismuth salt of claim 1 or a physiologically tolerable salt thereof to a host at risk for developing symptoms of such conditions.

18. A pharmaceutical composition for controlling conditions in which *H. pylori* is a causative factor, comprising an effective amount of at least one bismuth salt of claim 1 or of a physiologically tolerable salt thereof, together with a pharmaceutically tolerable excipient or auxiliary.



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CONTAINING VARIOUS ANTACIDS**application No. 09/389,211, filed on Sep. 2, 1999,  
now abandoned.(76) Inventors: **Daniel J. Zyck**, North Riverside, IL  
(US); **Michael J. Greenberg**,  
Northbrook, IL (US); **David G.**  
**Barkalow**, Deerfield, IL (US); **Scott W.**  
**Marske**, LaGrange, IL (US); **Phillip G.**  
**Schnell**, Downers Grove, IL (US);  
**Phillip Mazzone**, Griffith, IN (US)**Publication Classification**(51) Int. Cl.<sup>7</sup> ..... **A23G 3/30**  
(52) U.S. Cl. .... **426/3; 424/439; 426/103**Correspondence Address:  
**BRINKS HOFER GILSON & LIONE**  
**P.O. BOX 10395**  
**CHICAGO, IL 60610 (US)**(21) Appl. No.: **09/747,323**(22) Filed: **Dec. 22, 2000****Related U.S. Application Data**(63) Continuation-in-part of application No. 09/552,290,  
filed on Apr. 19, 2000, which is a continuation of(57) **ABSTRACT**

A method of making antacid coated chewing gum products comprises the steps of providing chewing gum cores; providing a coating syrup comprising a bulk sweetener and a neutralizing antacid suspended in the coating syrup, the coating syrup containing from about 25% to about 50% by weight of the solids in the syrup of a neutralizing antacid, selected from the group consisting of aluminum salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mixtures thereof, and applying the coating syrup to the cores and drying the syrup to produce a coating on the cores. Methods of use of the product to provide relief in the gastrointestinal tract are also included.

## COATED CHEWING GUM PRODUCTS CONTAINING VARIOUS ANTACIDS

### CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a continuation in part of the following applications: 1) U.S. patent application Ser. No. 09/552,290, filed Apr. 19, 2000, which is a continuation of U.S. patent application Ser. No. 09/389,211, filed Sep. 2, 1999; 2) PCT Application Serial No. US99/29,792, filed Dec. 14, 1999, designating the United States; 3) PCT Application Serial No. US99/29,742, filed Dec. 14, 1999, designating the United States; 4) U.S. patent application Ser. No. 09/591,256, filed Jun. 9, 2000; 5) U.S. patent application Ser. No. 09/654,464, filed Sep. 1, 2000; and 6) U.S. patent application Ser. No. 09/653,669, filed Sep. 1, 2000. Each of the foregoing applications are incorporated herein by reference.

### BACKGROUND OF THE INVENTION

[0002] The present invention relates to methods for producing coated chewing gum products. More particularly, the invention relates to producing coated chewing gum products containing a neutralizing antacid other than calcium carbonate and which is added to the chewing gum coating such that it will have a controlled fast release from chewing gum for maximum effectiveness.

[0003] Antacids are usually taken on an "as needed" basis to relieve gastrointestinal disturbances mostly due to dietary indiscretions. These antacids are generally insoluble inorganic salts such as calcium carbonate, magnesium carbonate, calcium hydroxide, magnesium hydroxide, or aluminum hydroxide. Antacids readily neutralize acids in the gastrointestinal (GI) tract and are commonly available in or as antacid tablets. Some typical consumer antacid products are: TUMS, which contains calcium carbonate; MILK of MAGNESIA, which contains magnesium hydroxide, and MAALOX PLUS, which contains a combination of aluminum hydroxide and magnesium hydroxide. Calcium carbonate is perhaps the most frequently used antacid. However, some individuals may not wish to ingest large doses of calcium. Calcium carbonate is also not the most effective antacid on a weight basis.

[0004] Coated chewing gum products are well known. Many prior art patents disclose chewing gum products coated with sugar sweeteners or polyol sweeteners. U.S. Pat. No. 4,317,838, for example, discloses a method of applying a sugarless coating to chewing gum. The coating may include calcium carbonate, talc or magnesium trisilicate as an anti-sticking agent. Synthetic sweeteners, including many different high-intensity sweeteners, are also suggested for use in the coating.

[0005] Another area of interest is the use of medicaments in chewing gum. In some instances, it is contemplated that an active medicament that is added to the chewing gum may be readily released. An active medicament may be added to the gum coating, which is a water soluble matrix, such that during the chewing period, the medicament may be released quickly, resulting in a fast release. This would allow a chewing gum coating to be a carrier for an active medicament, specifically an antacid with these fast release characteristics. For example, U.S. Pat. No. 4,867,989 discloses a

chewing gum composition coated with an outer shell containing layers of a mineral compound and a coating syrup, but this patent states that the mineral compound must be added separately and not dispersed in the syrup used to make the coating.

[0006] Previously, antacids have been added to chewing gum and in a chewing gum coating, but some products have not been totally consumer acceptable. The large amount of active antacid needed for effectiveness does not lend itself to giving a good tasting product. Also, the presence of sugar in the antacid chewing gum or coated on the chewing gum of some products is not consumer acceptable because sugar causes dental caries.

[0007] A sugarless coated chewing gum produced having calcium carbonate as an antacid in a sorbitol base coating is currently being sold under the trademark CHOOZ®. It has been found that by adding the antacid to a gum coating, the antacid is quickly released from the chewing gum into saliva and into the gastrointestinal (GI) tract. Relief from GI disturbances is quickly obtained, but does not last long.

[0008] It would be beneficial if antacids other than calcium carbonate could be administered in a form that was fast acting. It would be preferable to have not only fast relief, but relief of a longer duration. Thus, there is a need for a way to make coated chewing gum products that use an antacid other than calcium carbonate, and preferably provide antacid relief for a long duration, as well as being acceptable to the consumer from taste and other standpoints.

### SUMMARY OF THE INVENTION

[0009] It has been found that antacids, other than calcium carbonate, can be added as a suspension to the coating syrup to thus be included in the gum coating. These antacids will quickly dissipate to provide fast relief.

[0010] In a first aspect, the invention is a method of making antacid coated chewing gum products comprising the steps of: providing chewing gum cores; providing a coating syrup comprising a bulk sweetener and a neutralizing antacid suspended in the coating syrup, the coating syrup containing from about 25% to about 50% by weight of the solids in the syrup of a neutralizing antacid selected from the group consisting of aluminum salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mixtures thereof; and applying the coating syrup to the cores and drying the syrup to produce a coating on the cores.

[0011] In a preferred embodiment, the antacid has a particle size of greater than about 3 microns, which makes the antacid have a more prolonged period of relief.

[0012] In a second aspect, the invention is a method of delivering an antacid to an individual that provides relief in the gastrointestinal tract comprising the steps of: providing chewing gum cores; providing a coating syrup comprising a bulk sweetener and a neutralizing antacid suspended in the coating syrup, the coating syrup containing from about 25% to about 50% by weight of the solids in the syrup of a neutralizing antacid selected from the group consisting of aluminum salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mix-

tures thereof; applying the coating syrup to the cores and drying the syrup to produce a coating on the cores; and chewing the antacid coated chewing gum product in the mouth and swallowing the coating, the coating dispersing and dissolving to provide an antacid in the gastrointestinal tract.

[0013] Preferred embodiments of the invention include the addition of acid blockers such as histamine  $H_2$  - receptor antagonists. These agents inhibit or block the secretion of gastric acid by binding to a specific histamine receptor on the parietal (acid secreting) cell membranes located in the stomach. These agents, which may be added to the chewing gum center or to the antacid coating, are used for extended relief of gastrointestinal disturbances and extended relief from stomach acidity. Examples of histamine  $H_2$  - receptor antagonists are cimetidine, ranitidine and its active salt, nizatidine and famotidine, with famotidine being preferred.

[0014] It is believed that the neutralizing antacids other than calcium carbonate, when used in a coating made with a syrup having the antacid dispersed therein, will give a fast release of the antacid. In the preferred embodiment, providing a larger particle size antacid in a chewing gum coating makes it more effective and longer lasting. Thus, an advantage of a preferred embodiment of the present invention is administering an antacid to an individual that has a larger particle size than is typically administered orally, giving extended relief while still achieving the effect of fast relief.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0015] As used herein, the term "chewing gum" includes bubble gum and all other types of chewing gum. Unless specified otherwise, all percentages are weight percentages.

[0016] As mentioned above, products made by the present invention will include an antacid. The antacid will preferably be included as part of the coating syrup used to prepare a coated chewing gum product. A typical syrup may contain a polyol, suspended antacid, a binding agent, a high-intensity sweetener and a whitener.

[0017] In a preferred embodiment of the present invention, the antacid is contained in the coating of chewing gum products, which allows a chewing gum coating to be a carrier for the antacid. Accordingly, as the chewing gum is chewed, the active antacid in the gum coating is released into the saliva and ingested to give relief from gastrointestinal disturbances in the GI tract.

[0018] Antacid materials are given in the Merck Index or the Code of Federal Regulations. Such antacids, other than calcium carbonate, are suggested for use in this invention. These are listed below:

#### [0019] Aluminum salts

[0020] Alxitol sodium (aluminum sodium carbonate hexitol complex)

[0021] Almagate (carbonic acid, aluminum magnesium complex)

[0022] aluminum hydroxide

[0023] aluminum magnesium silicate

[0024] aluminum phosphate

[0025] basic aluminum carbonate gel (aluminum hydroxide-aluminum carbonate gel)

[0026] Sucralfate (basic aluminum sucrose sulfate complex)

[0027] dihydroxyaluminum aminoacetate

[0028] dihydroxyaluminum sodium carbonate

[0029] Magaldrate (aluminum magnesium hydroxide monohydrate)

#### [0030] Bismuth salts

[0031] bismuth aluminate

[0032] bismuth phosphate

[0033] bismuth carbonate

[0034] bismuth subcarbonate

[0035] bismuth subgallate

[0036] bismuth subnitrate

#### [0037] Magnesium salts

[0038] magnesium carbonate

[0039] magnesium hydroxide

[0040] magnesium oxide

[0041] magnesium peroxide

[0042] magnesium phosphate, tribasic

[0043] magnesium silicates (magnesium trisilicate)

[0044] magnesium aluminosilicates

#### [0045] Other Salts of Bicarbonate, Citrate, Phosphate, and Tartrate

[0046] sodium bicarbonate

[0047] potassium bicarbonate

[0048] potassium citrate

[0049] sodium potassium tartrate

[0050] tricalcium phosphate

[0051] The preferred antacids are generally carbonate or hydroxide salts of calcium, magnesium or aluminum, and are generally very water insoluble. When these materials are mixed with acids in the GI tract, the acids are readily neutralized to give relief from GI disturbances. Neutralizing antacids, which are insoluble inorganic salts, are known to neutralize stomach acidity very quickly. As a result, relief from gastrointestinal distress is fast and effective, but does not last long, possibly up to about 30 minutes. An acid blocker, when taken in combination with the antacid, will start to be effective after about 30 minutes, and be most effective after about 3-6 hours, and may last up to about 9-12 hours.

[0052] Examples of acid blockers are histamine  $H_2$  - receptor antagonists which include cimetidine, used in an over the counter (OTC) preparation called TAGAMET; famotidine, used in an OTC preparation called PEPICID; the hydrochloride salt of ranitidine, used in ZANTAC; and nizatidine, used in AXID. Some other types of acid blockers are called gastric proton pump inhibitors. These include omeprazole, used in PRILOSEC, and rabeprazole. All of

these have been used for the treatment of digestive disorders such as gastritis, dyspepsia, gastric hyperacidity, heartburn, gastric oppression and peptic ulcer.

[0053] Acid blockers may be added to a gum center, to a gum coating, or both the gum center and coating. A water-soluble acid blocker may be added to the gum center and release during chewing. Other acid blockers that may be water insoluble may need to be treated so as to allow their release from the chewing gum. These treatments may involve encapsulation, agglomeration, or entrapment of the acid blocker in a water-soluble matrix. Without a water-soluble matrix, the acid blocker may have an affinity for the gum base and not release for its intended effect.

[0054] Acid blockers may also be added to a chewing gum coating. If water soluble, the acid blocker may be added to the sugar or polyol syrup and applied throughout the coating process. Water insoluble acid blockers may be dissolved or dispersed in a solvent, possibly flavors, and applied at various times during the coating process. Preferably, the acid blocker may be added as a powder after it has been preblended with a dry charge material. This could allow more control of the level of the acid blocker used in the chewing gum product and may reduce any instability problems of the acid blocker that may be associated with moisture.

[0055] A dry pretreated acid blocker may be used that has been treated to give maximum stability. This pretreatment may include encapsulation, agglomeration, or entrapment of the acid blocker in a water soluble or water insoluble matrix necessary to give maximum stability of the acid blocker. This matrix may include materials that may control the release of the acid blockers in the stomach for maximum effectiveness. Stability of the acid blocker will be very important since the gum coating will also contain an effective amount of neutralizing antacid other than calcium carbonate, that will increase the pH of the coating, and which may effect the overall stability of the acid blocker.

[0056] The dosage level of acid blocker used in a preferred coated chewing gum product will vary depending on the acid blocker used. In general, the level of acid blocker will be about 1 mg to about 200 mg either in the gum center or preferably in a gum coating. This level of acid blocker is used in addition to a high level of antacid in the gum coating. The level of neutralizing antacid in the gum coating will be about 250 to 800 mg in 1 or 2 pieces of gum product having a weight of about 1.5 to 3 grams.

[0057] For antacid chewing gum products, magnesium hydroxide, magnesium carbonate and aluminum hydroxide are the most preferred antacid materials. The materials must be used in a gum coating to be most effective. Chewing gum bases that contain calcium carbonate or other antacids do not readily release the antacid during chewing. Since antacids are very water insoluble, they release from gum base either very slowly or over very long extended chewing. As a result, the materials mixed into the gum base are not effective as an antacid. Generally, when an antacid is added to a gum formulation separate from the gum base, the antacid becomes intimately mixed with the base during chewing and also releases slowly. However, when an antacid is used in the coating of the chewing gum, it does become quickly available in the oral cavity and is ingested to be an effective antacid.

[0058] Generally, suspension coatings with antacids for an antacid gum may be made with sugar. Sugar with its

naturally sweet taste masks some of the off-taste due to the use of high levels of antacid. With the advent of new coating technologies using less sweet sugarless polyols instead of sugar, the sweet taste of the coating is significantly reduced. In some coatings where xylitol is used, it is sufficiently sweet as a coating, but other polyols such as maltitol, hydrogenated isomaltulose, sorbitol, or erythritol, are not. When the coating contains high levels of antacids, the polyols generally lack sufficient sweetness to give a good tasting product. As a result, high-intensity sweeteners are preferably added to the coating containing antacids to give a high-quality, consumer-acceptable product.

[0059] For coated antacid chewing gum type products, the high level of antacid in the coating modifies the taste quality and gum texture. The addition of high-intensity sweeteners to the gum coating improves the taste of the finished product. This also occurs in sugar coated gums as well as polyol coated gums, so aspartame or another high-intensity sweeteners may also be added to sugar coated gums with antacids. If the high-intensity sweetener is subject to degradation, it may preferably be added as part of a different coating syrup from the coating syrup containing the antacid, as disclosed in U.S. patent application Ser. No. 09/591,256 filed Jun. 9, 2000, hereby incorporated by reference.

[0060] Since many of the neutralizing antacids are very water insoluble, the reaction rate of the salts with aqueous acids is dependant on the surface area of the neutralizing agent. Neutralizing agents with a large surface area will react faster with acids than those with a small surface area. Many smaller size particles with a combined large surface area neutralize acids faster than fewer large particles with a combined small surface area. However, larger particle sizes of antacids give longer lasting relief from stomach acidity. When the antacid particles are suspended in a coating syrup and applied as a gum coating, the particle sizes of antacid remains essentially the same throughout the process.

[0061] In studies performed using calcium carbonate but directed to determining the effect of particle size, analysis of a precipitated calcium carbonate having a median particle size of about 5 microns was done before and after being applied as a coating. Before coating, the sample was analyzed and found to have a median particle size of 5.1 microns. After preparing the sample of calcium carbonate in a suspension and applying it to a gum pellet for an antacid gum product, the particle size of the calcium carbonate was 4.9 microns.

[0062] It has been determined that a calcium carbonate having a median particle size of about 3 microns or greater is sufficient to give longer lasting relief of excess stomach activity. Other neutralizing antacids with a particle size of about 3 microns or greater should have a similar effect of giving long lasting relief from stomach acidity. Preferably the median particle size of the neutralizing antacid in the coating will be between about 3 microns and about 75 microns, and more preferably between about 3 microns and about 15 microns.

[0063] In terms of water solubility, larger particles have a tendency to dissolve more slowly in water, and as the neutralizing antacid dissolves, it neutralizes stomach acidity. Smaller particles of the neutralizing antacid could react faster, and larger particles would react slower.

[0064] In addition to the particle size of the antacid, different crystal structures have an effect on the rate of

dissolution and the rate of neutralization. For example, natural forms of calcium carbonate such as Calcite, Aragonite, and Vaterite are highly crystalline forms of calcium carbonate and could dissolve more slowly. Marble, Dolomite, and even Mollusk shells are made of amorphous forms of calcium carbonate, and could dissolve faster. Precipitated calcium carbonate, which is purified from natural sources, is a "micro" crystalline form and would dissolve quickly and neutralizes acidity quickly. Neutralizing antacids other than calcium carbonate, for use in the present invention, may have similar forms and react similarly.

[0065] In general, a chewing gum composition typically comprises a water-soluble bulk portion, a water-insoluble chewable gum base portion and typically water-insoluble flavoring agents. The water-soluble portion dissipates with a portion of the flavoring agent over a period of time during chewing. The gum base portion is retained in the mouth throughout the chew.

[0066] The insoluble gum base generally comprises elastomers, resins, fats and oils, softeners and inorganic fillers. The gum base may or may not include wax. The insoluble gum base can constitute approximately 5% to about 95% by weight of the chewing gum, more commonly the gum base comprises about 10% to about 50% of the gum, and in some preferred embodiments approximately 25% to about 35% by weight, of the chewing gum. In pellet gum center formulations, the level of insoluble gum base may be much higher.

[0067] In a preferred embodiment, the chewing gum base of the present invention contains about 20% to about 60% by weight synthetic elastomer, about 0% to about 30% by weight natural elastomer, about 5% to about 55% by weight elastomer plasticizer, about 4% to about 35% by weight filler, about 5% to about 35% by weight softener, and optional minor amounts (about 1% or less by weight) of miscellaneous ingredients such as colorants, antioxidants, etc.

[0068] Synthetic elastomers may include, but are not limited to, polyisobutylene with GPC weight average molecular weights of about 10,000 to about 95,000, isobutylene-isoprene copolymer (butyl elastomer), styrene-butadiene, copolymers having styrene-butadiene ratios of about 1:3 to about 3:1, polyvinyl acetate having GPC weight average molecular weights of about 2,000 to about 90,000, polyisoprene, polyethylene, vinyl acetate - vinyl laurate copolymers having vinyl laurate contents of about 5% to about 50% by weight of the copolymer, and combinations thereof. Preferred ranges are: 50,000 to 80,000 GPC weight average molecular weight for polyisobutylene; 1:1 to 1:3 bound styrene-butadiene for styrene-butadiene; 10,000 to 65,000 GPC weight average molecular weight for polyvinyl acetate, with the higher molecular weight polyvinyl acetates typically used in bubble gum base; and a vinyl laurate content of 10-45% for vinyl acetate-vinyl laurate.

[0069] Natural elastomers may include natural rubber such as smoked or liquid latex and guayule, as well as natural gums such as jelutong, lechi caspi, perillo, sorva, massaranduba balata, massaranduba chocolate, nispero, ros-indinha, chicle, gutta hang kang, and combinations thereof. The preferred synthetic elastomer and natural elastomer concentrations vary depending on whether the chewing gum in which the base is used is adhesive or conventional, bubble

gum or regular gum, as discussed below. Preferred natural elastomers include jelutong, chicle, sorva and massaranduba balata.

[0070] Elastomer plasticizers may include, but are not limited to, natural rosin esters such as glycerol esters or partially hydrogenated rosin, glycerol esters of polymerized rosin, glycerol esters of partially dimerized rosin, glycerol esters of rosin, pentaerythritol esters of partially hydrogenated rosin, methyl and partially hydrogenated methyl esters of rosin, pentaerythritol esters of rosin; synthetics such as terpene resins derived from alpha-pinene, beta-pinene, and/or d-limonene; and any suitable combinations of the foregoing. The preferred elastomer plasticizers will also vary depending on the specific application, and on the type of elastomer which is used.

[0071] Fillers/texturizers may include magnesium and calcium carbonate, ground limestone, silicate types such as magnesium and aluminum silicate, clay, alumina, talc, titanium oxide, mono-, di- and tri-calcium phosphate, cellulose polymers, such as wood, and combinations thereof.

[0072] Softeners/emulsifiers may include tallow, hydrogenated tallow, hydrogenated and partially hydrogenated vegetable oils, cocoa butter, glycerol monostearate, glycerol triacetate, lecithin, mono-, di- and triglycerides, acetylated monoglycerides, fatty acids (e.g. stearic, palmitic, oleic and linoleic acids), and combinations thereof.

[0073] Colorants and whiteners may include FD&C-type dyes and lakes, fruit and vegetable extracts, titanium dioxide, and combinations thereof.

[0074] The base may or may not include wax. An example of a wax-free gum base is disclosed in U.S. Pat. No. 5,286,500, the disclosure of which is incorporated herein by reference.

[0075] In addition to a water-insoluble gum base portion, a typical chewing gum composition includes a water-soluble bulk portion and one or more flavoring agents. The water-soluble portion can include bulk sweeteners, high-intensity sweeteners, flavoring agents, softeners, emulsifiers, colors, acidulants, fillers, antioxidants, and other components that provide desired attributes.

[0076] Softeners are added to the chewing gum in order to optimize the chewability and mouth feel of the gum. The softeners, which are also known as plasticizers and plasticizing agents, generally constitute between approximately 0.5% to about 15% by weight of the chewing gum. The softeners may include glycerin, lecithin, and combinations thereof. Aqueous sweetener solutions such as those containing sorbitol, hydrogenated starch hydrolysates, corn syrup and combinations thereof, may also be used as softeners and binding agents in chewing gum.

[0077] Bulk sweeteners include both sugar and sugarless components. Bulk sweeteners typically constitute about 5% to about 95% by weight of the chewing gum, more typically, about 20% to about 80% by weight, and more commonly, about 30% to about 60% by weight of the gum. Sugar sweeteners generally include saccharide-containing components commonly known in the chewing gum art, including but not limited to, sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, galactose, corn syrup solids, and the like, alone or in combination. Sugarless sweeteners include,



but are not limited to, sugar alcohols such as sorbitol, mannitol, xylitol, hydrogenated starch hydrolysates, maltitol, and the like, alone or in combination.

[0078] High-intensity artificial sweeteners can also be used, alone or in combination, with the above. Preferred sweeteners include, but are not limited to, sucralose, aspartame, N-substituted APM derivatives such as neotame, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones, thaumatin, monellin, and the like, alone or in combination. In order to provide longer lasting sweetness and flavor perception, it may be desirable to encapsulate or otherwise control the release of at least a portion of the artificial sweetener. Such techniques as wet granulation, wax granulation, spray drying, spray chilling, fluid bed coating, coacervation, and fiber extrusion may be used to achieve the desired release characteristics.

[0079] Combinations of sugar and/or sugarless sweeteners may be used in chewing gum. Additionally, the softener may also provide additional sweetness such as with aqueous sugar or alditol solutions.

[0080] If a low calorie gum is desired, a low caloric bulking agent can be used. Examples of low caloric bulking agents include: polydextrose; oligofructose (Raftilose); inulin (Raftilin); fructooligosaccharides (NutraFlora); palatinose oligosaccharide; guar gum hydrolysate (BeneFiber); or indigestible dextrin (Fibersol). However, other low caloric bulking agents can be used.

[0081] A variety of flavoring agents can also be used, if desired. The flavor can be used in amounts of about 0.1 to about 15 weight percent of the gum, and preferably, about 0.2% to about 5% by weight. Flavoring agents may include essential oils, synthetic flavors or mixtures thereof including, but not limited to, oils derived from plants and fruits such as citrus oils, fruit essences, peppermint oil, spearmint oil, other mint oils, clove oil, oil of wintergreen, anise and the like. Artificial flavoring agents and components may also be used. Natural and artificial flavoring agents may be combined in any sensorially acceptable fashion.

[0082] In general, chewing gum is manufactured by sequentially adding the various chewing gum ingredients to a commercially available mixer known in the art. After the ingredients have been thoroughly mixed, the gum mass is discharged from the mixer and shaped into the desired form, such as rolling into sheets and cutting into sticks, extruding into chunks or casting into pellets, which are then coated or panned.

[0083] Generally, the ingredients are mixed by first melting the gum base and adding it to the running mixer. The base may also be melted in the mixer itself. Color or emulsifiers may also be added at this time. A softener such as glycerin may also be added at this time, along with syrup and a portion of the bulking agent. Further parts of the bulking agent are added to the mixer. Flavoring agents are typically added with the final portion of the bulking agent. Other optional ingredients are added to the batch in a typical fashion, well known to those of ordinary skill in the art.

[0084] The entire mixing procedure typically takes from five to fifteen minutes, but longer mixing times may sometimes be required. Those skilled in the art will recognize that many variations of the above described procedure may be followed.

[0085] After the ingredients are mixed, the gum mass is formed into pellets or balls. Pellet or ball gum is prepared as conventional chewing gum but formed into pellets that are pillow shaped, or into balls. The pellets/balls are used as cores for the coated product. The cores can be sugar or polyol coated or panned by conventional panning techniques to make a unique coated pellet gum. The weight of the coating may be about 20% to about 50% of the weight of the finished product, but may be as much as 75% of the total gum product.

[0086] Conventional panning procedures generally coat with sucrose, but recent advances in panning have allowed use of other carbohydrate materials to be used in place of sucrose. Some of these materials include, but are not limited to, sugars such as dextrose, maltose, isomaltulose, and tagatose, or sugarless bulk sweeteners such as xylitol, sorbitol, lactitol, hydrogenated isomaltulose, erythritol, maltitol, and other new polyols (also referred to as alditols) or combinations thereof. The coating is preferably sugarless. A preferred coating comprises about 30% to about 75% maltitol. These materials may be blended with panning modifiers including, but not limited to, gum arabic, gum talha, maltodextrins, corn syrup, gelatin, cellulose type materials like carboxymethyl cellulose or hydroxymethyl cellulose, starch and modified starches, vegetables gums like alginates, locust bean gum, guar gum, and gum tragacanth. Antitack agents may also be added as panning modifiers, which allow the use of a variety of carbohydrates and sugar alcohols. Flavors may also be added with the sugar or sugarless coating to yield unique product characteristics.

[0087] As noted above, the coating may contain ingredients such as flavoring agents, as well as dispersing agents, coloring agents, film formers and binding agents. Flavoring agents contemplated by the present invention include those commonly known in the art such as essential oils, synthetic flavors or mixtures thereof, including but not limited to oils derived from plants and fruits such as citrus oils, fruit essences, peppermint oil, spearmint oil, other mint oils, clove oil, oil of wintergreen, anise and the like. The flavoring agents may be used in an amount such that the coating will contain from about 0.2% to about 3% flavoring agent, and preferably from about 0.7% to about 2.0% flavoring agent.

[0088] High-intensity sweeteners contemplated for use in the coating include but are not limited to synthetic substances, such as saccharin, thaumatin, alitame, saccharin salts, aspartame, N-substituted APM derivatives such as neotame, sucralose, cyclamic acids and its salts, glycyrrhizin, dihydrochalcones, monellin and acesulfame-K or other salts of acesulfame. The high-intensity sweetener may be added to the coating syrup in an amount such that the coating will contain from about 0.01% to about 2.0%, and preferably from about 0.1% to about 1.0% high-intensity sweetener. Preferably the high-intensity sweetener is not encapsulated.

[0089] Dispersing agents are often added to syrup coatings for the purpose of whitening and tack reduction. Dispersing agents contemplated by the present invention to be employed in the coating syrup include titanium dioxide, talc, or any other antistick compound. Titanium dioxide is a presently preferred dispersing agent of the present invention. The dispersing agent may be added to the coating syrup in

amounts such that the coating will contain from about 0.1% to about 1.0%, and preferably from about 0.3% to about 0.6% of the agent.

[0090] When high amounts of antacid is used, the neutralizing antacid is dispersed or suspended in the coating syrup that contains the sugar or polyol, thus making a syrup suspension. Generally, as the level of neutralizing antacid is increased, the level of sugar or polyol is decreased. Levels of antacid used may be as low as 25% of the total solids or as high as 50% of the total solids in the syrup, and more preferably will comprise about 30% to about 40% of the total solids. In preferred embodiments, the antacid will comprise about 25% to about 50% of the gum coating, and more preferably about 30% to about 40% of the gum coating.

[0091] Coloring agents are preferably added directly to the syrup suspension in the dye or lake form. Coloring agents contemplated by the present invention include food quality dyes. Film formers preferably added to the syrup include methyl cellulose, gelatins, hydroxypropyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose and the like and combinations thereof. Binding agents may be added either as an initial coating on the chewing gum center or may be added directly into the syrup. Binding agents contemplated by the present invention include gum arabic, gum talha, guar gum, karaya gum, locust bean gum, alginate gums, xanthan gum, arabinogalactan, various cellulose derivatives, vegetable gums, gelatin and mixtures thereof, with gum arabic being preferred. The binding agent is preferably used at a level of at least about 2% of the coating syrup.

[0092] The coating is initially present as a liquid syrup which contains from about 30% to about 80% of the coating ingredients previously described herein, and from about 20% to about 70% of a solvent such as water. In general, the coating process is carried out in a rotating pan. Sugar or sugarless gum center tablets to be coated are placed into the rotating pan to form a moving mass. The material or syrup suspension which will eventually form the coating is applied or distributed over the gum center tablets. Flavoring agents may be added before, during and after applying the syrup suspension to the gum centers. Once the coating has dried to form a hard surface, additional syrup additions can be made to produce a plurality of coatings or multiple layers of hard coating.

[0093] In a hard coating panning procedure, syrup is added to the gum center tablets at a temperature range of from about 100° F. (38° C.) to about 240° F. (116° C.). Preferably, the syrup temperature is from about 130° F. (54° C.) to about 200° F. (94° C.) throughout the process in order to prevent the polyol or sugar in the syrup suspension from crystallizing. The syrup suspension may be mixed with, sprayed upon, poured over, or added to the gum center tablets in any way known to those skilled in the art.

[0094] In general, a plurality of layers is obtained by applying single coats, allowing the layers to dry, and then repeating the process. The amount of solids added by each coating step depends chiefly on the concentration of the coating syrup suspension. Any number of coats may be applied to the gum center tablet. Preferably, no more than about 75-100 coats are applied to the gum center tablets. The

present invention contemplates applying an amount of syrup sufficient to yield a coated comestible containing about 20% to about 75% coating.

[0095] Those skilled in the art will recognize that in order to obtain a plurality of coated layers, a plurality of premeasured aliquots of coating syrup suspension may be applied to the gum center tablets. It is contemplated, however, that the volume of aliquots of syrup suspension applied to the gum center tablets may vary throughout the coating procedure.

[0096] Once a coating is applied to the gum center tablets, the present invention contemplates drying the wet syrup suspension in an inert medium. A preferred drying medium comprises air. Preferably, forced drying air contacts the wet syrup coating in a temperature range of from about 70° F. (21° C.) to about 115° F. (46° C.). More preferably, the drying air is in the temperature range of from about 80° F. (27° C.) to about 100° F. (38° C.). The invention also contemplates that the drying air possess a relative humidity of less than about 15 percent. Preferably, the relative humidity of the drying air is less than about 8 percent.

[0097] The drying air may be passed over and admixed with the syrup coated gum centers in any way commonly known in the art. Preferably, the drying air is blown over and around or through the bed of the syrup coated gum centers at a flow rate, for large scale operations, of about 2800 cubic feet per minute. If lower quantities of material are being processed, or if smaller equipment is used, lower flow rates would be used.

[0098] The present invention also contemplates the application of powder material after applying an aliquot of coating syrup to help build up the coating.

[0099] In addition to applying a plurality of liquid layers and drying with air, a dry charge material may be added to dry the coating applications. This is especially useful when coating with some sugars and polyols, such as dextrose, sorbitol, maltitol, and hydrogenated isomaltulose. A liquid addition of coating syrup is made in the coating process and after a specified time to allow the liquid to spread evenly over the pieces, a dry powder material is applied. This also helps to dry the liquid coating. This is referred to as dry charging and is commonly used in "soft" panning operations and is commonly known by those skilled in the art. The dry charge material may consist mostly of the sugar or polyol used in the liquid coating, but may also contain other additives such as gums, dispersing agents, and antitack agents. The acid blocker could be preblended with the dry charge material and applied in about 3 to 12 dry charge applications. After a dry charge application, 2 to 4 liquid applications are made to cover the dry charge material.

[0100] When flavors are added to a sugar or sugarless coating of pellet gum, the flavors are generally preblended with the coating syrup just prior to applying it to the core or added together to the core in one or more coating applications in a revolving pan containing the cores. Generally, the coating syrup is very hot, about 130° F. (54° C.) to 200° F. (93° C.), and the flavor may volatilize if preblended with the coating syrup too early.

[0101] The coating syrup is preferably applied to the gum cores as a hot liquid, the sugar or polyol allowed to crystallize, and the coating then dried with warm, dry air. Aliquots of syrups are preferably applied in about 30 to 80

applications to obtain a hard shell coated product having an increased weight gain of about 20% to 75%. A flavor is applied with one, two, three or even four or more of these coating applications. Each time flavor is added, several non-flavored coatings are applied to cover the flavor before the next flavor coat is applied. This reduces volatilization of the flavor during the coating process.

[0102] For mint flavors such as spearmint, peppermint and wintergreen, some of the flavor components are volatilized, but sufficient flavor remains to give a product having a strong, high impact flavor. Fruit flavors, that may contain esters, are more easily volatilized and may be flammable and/or explosive and therefore, generally these type of fruit flavors are not used in coatings.

### EXAMPLES

[0103] The following examples of the invention are provided by way of explanation and illustration.

[0104] As noted earlier, the gum formulas can be prepared as sugar or sugarless type formulations and made in a pellet or pillow shape or a round ball or any other shape of product for coating/panning. However, gum formulas for pellet centers are generally adjusted to a higher level of gum base to give a more consumer acceptable size of gum bolus.

[0105] Keeping this in mind, if a coating of about 25% of the total product is added to a pellet core as sugar or polyols, the gum base in the pellet core should also be increased by 25%. Likewise, if a 33% coating is applied, the base levels should also be increased by 33%. As a result, gum centers are usually formulated with about 25% to about 50% gum base with a corresponding decrease in the other ingredients except flavor. Even higher levels of base may be used in the present invention since an antacid is added to a pellet coating. Generally flavor levels in the gum increase with the level of gum base as the base tends to bind flavors into the gum and more flavor is needed to give a good flavorful product. However flavors can also be added to the coating to give increased flavor impact and more flavor perception.

[0106] Some typical sugarless gum center formulations are shown in Table 1 that can be used as centers that are coated with a coating containing a neutralizing antacid other than calcium carbonate to give an effective antacid.

TABLE 1

| (WEIGHT PERCENT) |       |       |       |       |       |       |
|------------------|-------|-------|-------|-------|-------|-------|
|                  | EX. 1 | EX. 2 | EX. 3 | EX. 4 | EX. 5 | EX. 6 |
| SUGAR            | 48.0  | 47.0  | 46.0  | 40.0  | 38.0  | 35.0  |
| GUM BASE         | 30.0  | 35.0  | 40.0  | 30.0  | 35.0  | 40.0  |
| CORN SYRUP       | 20.0  | 15.0  | 12.0  | 18.0  | 14.0  | 12.0  |
| GLYCERIN         | 1.0   | 1.0   | 1.0   | 1.0   | 1.0   | 1.0   |
| PEPPERMINT       | 1.0   | 1.0   | 1.0   | 1.0   | 1.0   | 1.0   |
| FLAVOR           |       |       |       |       |       |       |
| DEXTROSE         | —     | —     | —     | 10.0  | 10.0  | 10.0  |
| MONOHYDRATE      |       |       |       |       |       |       |
| ACID BLOCKER     | —     | 1.0   | —     | —     | 1.0   | 1.0   |

[0107] Higher levels of base may be used with a corresponding decrease in other ingredients. Also, other sugars may be used in the gum center.

[0108] A neutralizing antacid can then be used in the coating formula on the various pellet gum formulations. The

following Table 2 shows some sugar and dextrose type coating formulas: Using a 1 gram center, the levels of antacid in the following tables will give 250-800 mg per 1 or 2 pieces in 1.5-3.0 gram pieces with 33% to 66% coating. The level of antacid blocker in the center is 10 mg for a 1 gram center. Coating formulas below with acid blocker in the center with a 50% coating will give 20 mg of acid blocker in a 2 gram piece. Examples without acid blocker in the center, and only in the coating, will give 10 mg acid blocker in a 2 gram coated gum piece.

TABLE 2

| (DRY WEIGHT PERCENT) |        |        |        |        |        |        |
|----------------------|--------|--------|--------|--------|--------|--------|
|                      | EX. 7  | EX. 8  | EX. 9  | EX. 10 | EX. 11 | EX. 12 |
| SUGAR                | 72.0   | 64.3   | 53.0   | 72.3   | 65.0   | 55.5   |
| GUM ARABIC           | 2.0    | 3.0    | 4.0    | 2.0    | 3.0    | 4.0    |
| TITANIUM             | 0.5    | 1.0    | 1.0    | —      | —      | —      |
| DIOXIDE              |        |        |        |        |        |        |
| MAGNESIUM            | 25.0   | —      | 20.0   | 25.0   | —      | 20.0   |
| CARBONATE            |        |        |        |        |        |        |
| MAGNESIUM            | —      | 30.0   | 20.0   | —      | 30.0   | 20.0   |
| HYDROXIDE            |        |        |        |        |        |        |
| FLAVOR               | 0.3    | 0.5    | 0.8    | 0.5    | 0.8    | 0.3    |
| WAX                  | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| ACESULFAME K         | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| ACID BLOCKER         | —      | 1.0    | 1.0    | —      | 1.0    | —      |
|                      | EX. 13 | EX. 14 | EX. 15 | EX. 16 |        |        |
| DEXTROSE             | 72.4   | 64.2   | 73.0   | 55.3   |        |        |
| MONOHYDRATE          |        |        |        |        |        |        |
| GUM ARABIC           | 1.5    | 3.0    | 1.5    | 3.0    |        |        |
| TITANIUM             | 0.5    | 1.0    | —      | —      |        |        |
| DIOXIDE              |        |        |        |        |        |        |
| MAGNESIUM            | 25.0   | —      | 25.0   | 30.0   |        |        |
| CARBONATE            |        |        |        |        |        |        |
| ALUMINUM             | —      | 30.0   | —      | 10.0   |        |        |
| HYDROXIDE            |        |        |        |        |        |        |
| FLAVOR               | 0.3    | 0.5    | 0.2    | 0.4    |        |        |
| WAX                  | 0.1    | 0.1    | 0.1    | 0.1    |        |        |
| ACESULFAME K         | 0.2    | 0.2    | 0.2    | 0.2    |        |        |
| ACID BLOCKER         | —      | 1.0    | —      | 1.0    |        |        |

[0109] The above formulations are made by making a first coating syrup by dissolving the sugar or dextrose monohydrate and gum arabic in solution at boiling, and suspending titanium dioxide and/or antacid in this syrup. When used, the acid blocker may be dispersed in the coating syrup. Flavor is not mixed with the hot syrup, but added at low levels with one or more coats. Acesulfame K may be added as part of the coating syrup. After the final coats are applied and dried, wax is applied to give a smooth polish.

[0110] The above process gives a hard shell coating. Often a dry charge of powdered sugar or dextrose monohydrate may be used. This gives a somewhat softer coating. A dry charge may be used to build up a coating, but then finished with a straight syrup to obtain a hard shell. Table 3 gives these types of formulas.

TABLE 3

| (DRY WEIGHT PERCENT) |        |        |        |        |        |        |
|----------------------|--------|--------|--------|--------|--------|--------|
|                      | EX. 17 | EX. 18 | EX. 19 | EX. 20 | EX. 21 | EX. 22 |
| SUGAR*               | 62.4   | 50.3   | —      | —      | 52.4   | —      |
| DEXTROSE             | —      | —      | 62.2   | 50.0   | —      | 40.8   |
| MONO-HYDRATE*        |        |        |        |        |        |        |

powder is dry charged after a gum arabic solution is applied in the first stages of coating, which is then followed by a hard shell coating of sugar solution or dextrose solution.

[0112] Gum arabic may also be used in coating of sugarless gum centers. Like sugar gum centers, the base formulation can be increased in proportion to the amount of coating applied to the center. Generally, the base level may be increased to 30-46% with the other ingredients proportionally reduced. Some typical gum formulas are in Table 4.

TABLE 4

|                                       | <u>(WEIGHT PERCENT)</u> |        |        |        |        |                   |                    |
|---------------------------------------|-------------------------|--------|--------|--------|--------|-------------------|--------------------|
|                                       | EX. 23                  | EX. 24 | EX. 25 | EX. 26 | EX. 27 | EX. 28            | EX. 29             |
| GUM BASE                              | 35.0                    | 35.0   | 30.0   | 35.0   | 30.0   | 40.0              | 35.8               |
| CALCIUM CARBONATE <sup>b)</sup>       | —                       | —      | 5.0    | 15.0   | 10.0   | —                 | 14.5               |
| SORBITOL                              | 43.1                    | 43.9   | 45.0   | 43.1   | 49.8   | 40.0              | 40.6               |
| MANNITOL                              | 10.0                    | 10.0   | 5.0    | —      | —      | 8.0               | —                  |
| GLYCERIN                              | —                       | 8.0    | 2.0    | 3.0    | 8.0    | 2.0               | 3.0                |
| SORBITOL LIQUID                       | 10.0                    | —      | 10.0   | —      | —      | 6.0 <sup>b)</sup> | 1.05 <sup>c)</sup> |
| FLAVOR                                | 1.5                     | 1.5    | 1.5    | 2.5    | 2.0    | 2.0               | 2.5                |
| ENCAPSULATED HIGH-INTENSITY SWEETENER | 0.4                     | 0.4    | 0.5    | 1.0    | 0.2    | 0.6               | 2.0                |
| LECITHIN                              | —                       | 0.2    | —      | 0.4    | —      | 0.4               | 0.55               |
| ACID BLOCKER                          | —                       | 1.0    | 1.0    | —      | —      | 1.0               | —                  |

<sup>a)</sup>Lycasin brand hydrogenated starch hydrolyzate is used instead of sorbitol liquid.

<sup>b)</sup>This material is base filler and may not release to give an antacid effect.

<sup>c)</sup>Water is added in place of sorbitol liquid.

TABLE 3-continued

| (DRY WEIGHT PERCENT) |        |        |        |        |        |        |
|----------------------|--------|--------|--------|--------|--------|--------|
|                      | EX. 17 | EX. 18 | EX. 19 | EX. 20 | EX. 21 | EX. 22 |
| POWDER               | 10.0   | 5.0    | —      | —      | —      | —      |
| SUGAR**              | —      | —      | 10.0   | 5.0    | 10.0   | 5.0    |
| POWDER               | —      | —      | 10.0   | 5.0    | 10.0   | 5.0    |
| DEXTROSE**           | —      | —      | 10.0   | 5.0    | 10.0   | 5.0    |
| GUM ARABIC           | 2.0    | 3.0    | 2.0    | 3.0    | 8.0    | 8.0    |
| POWDER               | —      | —      | —      | —      | 4.0    | 4.0    |
| GUM ARABIC SOLUTION  | —      | —      | —      | —      | 4.0    | 4.0    |
| FLAVOR               | 0.4    | 0.5    | 0.4    | 0.6    | 0.4    | 0.8    |
| WAX                  | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| MAGNESIUM CARBONATE  | 25.0   | 40.0   | —      | —      | —      | —      |
| MAGNESIUM HYDROXIDE  | —      | —      | 25.0   | 40.0   | —      | —      |
| ALUMINUM HYDROXIDE   | —      | —      | —      | —      | 25.0   | 40.0   |
| ACESULFAME K         | 0.1    | 0.1    | 0.3    | 0.3    | 0.1    | 0.3    |
| ACID BLOCKER**       | —      | 1.0    | —      | 1.0    | —      | 1.0    |

\*Powder and/or crystalline sugar along with gum arabic may be blended with antacid or antacid may be suspended in the sugar or dextrose syrup.

\*\*Acid blocker is preblended with powder sugar or dextrose before use.

[0111] In Examples 17-20, gum arabic is blended in the sugar/dextrose syrup. In Examples 21 and 22, gum arabic

[0113] In the above center formulations, the high-intensity sweetener used is aspartame, acesulfame K, or a combination thereof. However other high-intensity sweeteners such as alitame, salts of acesulfame, cyclamate and its salts, saccharin and its salts, neotame, sucralose, thaumatin, monellin, dihydrochalcones, stevioside, glycyrrhizin and combinations thereof may be used in any of the examples with the level adjusted for sweetness.

[0114] Lycasin and other polyols such as maltitol, xylitol, erythritol, lactitol and hydrogenated isomaltulose may also be used in the gum center formulations at various levels. The texture may be adjusted by varying glycerin or sorbitol liquid. Sweetness of the center formulation can also be adjusted by varying the level of high-intensity sweetener.

[0115] Neutralizing antacids can be used in sugarless coatings with xylitol, sorbitol, maltitol, lactitol, hydrogenated isomaltulose and erythritol. Gum talba acts as a binding agent, film former and hardener of the coated pellet. Using a 1 gram center, the levels of antacid in the following tables will give 250-800 mg of antacid per 1 or 2 pieces in 1.5-3.0 gram chewing gum product pieces with 33% to 66% coating. The level of acid blocker in the center is 10 mg for a 1 gram center. Coating formulas below with acid blocker in the center with a 50% coating will give 20 mg of acid blocker in a 2 gram piece. Examples without acid blocker in the center, and only in the coating, will give 10 mg acid blocker in a 2-gram coated gum piece.

TABLE 5

|                     | (DRY WEIGHT PERCENT) |        |        |        |        |        |
|---------------------|----------------------|--------|--------|--------|--------|--------|
|                     | EX. 30               | EX. 31 | EX. 32 | EX. 33 | EX. 34 | EX. 35 |
| XYLITOL**           | 69.6                 | 51.1   | 65.5   | 49.3   | 65.2   | 48.0   |
| GUM ARABIC          | 4.0                  | 6.0    | 7.0    | 8.5    | 8.5    | 10.0   |
| FLAVOR              | 0.5                  | 0.5    | 0.7    | 0.7    | 0.9    | 0.5    |
| TITANIUM DIOXIDE    | 0.5                  | 0.9    | —      | —      | —      | —      |
| TALC                | 0.1                  | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| WAX                 | 0.1                  | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| COLOR*              | —                    | —      | 1.4    | —      | —      | —      |
| MAGNESIUM HYDROXIDE | 25.0                 | 40.0   | —      | 20.0   | —      | —      |
| MAGNESIUM CARBONATE | —                    | —      | 25.0   | —      | —      | 20.0   |
| ALUMINUM HYDROXIDE  | —                    | —      | —      | 20.0   | 25.0   | 20.0   |
| ACESULFAME K        | 0.2                  | 0.3    | 0.2    | 0.3    | 0.2    | 0.3    |
| ACID BLOCKER**      | —                    | 1.0    | —      | 1.0    | —      | 1.0    |

\*Lake color dispersed in xylitol solution.

\*\*Acid blocker may be dissolved or dispersed in xylitol syrup.

[0116] The above formulas are used to coat pellets by applying a xylitol/gum arabic syrup in multiple coats and air drying. Color or titanium dioxide is also mixed in the xylitol/gum arabic syrup. Neutralizing antacids may be suspended in the xylitol hot syrup or added as a dry powder between syrup applications. Acesulfame K may be added as part of the coating syrup. After the pellets have been coated and dried, talc and wax are added to give a polish.

[0117] Like xylitol, maltitol coatings may also contain a combination of antacid materials and acid blocker. The following formulation can be made.

TABLE 6

|                     | (DRY WEIGHT PERCENT) |        |        |        |        |        |
|---------------------|----------------------|--------|--------|--------|--------|--------|
|                     | EX. 36               | EX. 37 | EX. 38 | EX. 39 | EX. 40 | EX. 41 |
| MALTTTOL            | 68.5                 | 49.5   | 60.8   | 50.4   | 59.8   | 45.1   |
| MALTTTOL POWDER     | 3.0                  | 5.0    | 6.0    | 5.0    | 10.0   | 6.0    |
| GUM TALHA           | 2.0                  | 4.0    | 6.0    | 2.0    | 3.0    | 6.0    |
| FLAVOR              | 0.5                  | 0.4    | 0.7    | 0.5    | 0.3    | 1.0    |
| TITANIUM DIOXIDE    | 0.5                  | 0.5    | 1.0    | 0.5    | 0.4    | 1.3    |
| TALC                | 0.1                  | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| WAX                 | 0.1                  | 0.1    | 0.1    | 0.1    | 0.1    | 0.1    |
| MAGNESIUM HYDROXIDE | —                    | 20.0   | 25.0   | —      | —      | 20.0   |
| MAGNESIUM CARBONATE | 25.0                 | 20.0   | —      | 20.0   | —      | —      |
| ALUMINUM HYDROXIDE  | —                    | —      | —      | 20.0   | 25.0   | 20.0   |
| ACESULFAME K        | 0.3                  | 0.4    | 0.3    | 0.4    | 0.3    | 0.4    |
| ACID BLOCKER        | —                    | —      | —      | 1.0    | 1.0    | —      |

[0118] Maltitol powder with the acid blocker is used to dry charge in the early stages of coating. Maltitol, gum talha, neutralizing antacid, and titanium dioxide are blended into the coating syrup and applied to the gum pellets. The mixture is applied as a syrup suspension. After all coating is applied and dried, talc and wax are added to give a polish.

[0119] In a similar manner, coatings with sorbitol, lactitol and hydrogenated isomaltulose may be made in the coating formulas in Table 6 by replacing maltitol with any one of the other polyols and maltitol powder with the polyol powder. Like maltitol, the other polyols may become sticky during the coating and drying process, so the dry powder charge may be needed to give the proper drying. In the later stages of the coating process, less gum talha could be used and a more pure polyol syrup could be used to give a smooth surface. Also, the dry charge would probably only be used in the early stages of the coating process.

[0120] In addition to dry charging with the specific polyol, other ingredients may be added to the dry charge to help absorb moisture. These materials could be inert such as talc, magnesium carbonate, starches, gums like arabinogalactan, gum talha, gum arabic or other moisture absorbing materials. Also, powdered sweeteners or flavors could be added with the dry charge.

[0121] Polyols such as sorbitol, maltitol, lactitol and hydrogenated isomaltulose are not sufficiently sweet compared to sugar or xylitol, so high-intensity sweeteners are preferably added to the coating. Beside aspartame, other high-intensity sweeteners may also be used such as acesulfame K, salts of acesulfame, cyclamate and its salts, saccharin and its salts, alitame, sucralose, thaumatin, monellin, dihydrochalcones, glycyrrhizin, neotame, and combinations thereof. When adding antacids other than calcium carbonate, and a hot syrup is applied, heat and high pH may degrade some sweeteners, so only stable high-intensity sweeteners should be used if the high-intensity sweetener is added in the main coating syrup.

[0122] It should be appreciated that the compositions and methods of the present invention are capable of being incorporated in the form of a variety of embodiments, only a few of which have been illustrated and described above. The invention may be embodied in other forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive, and the scope of the invention, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

1. A method of making antacid coated chewing gum products comprising the steps of:

a) providing chewing gum cores;

b) providing a coating syrup comprising:

i) a bulk sweetener and

ii) a neutralizing antacid suspended in the coating syrup; the coating syrup containing from about 25% to about 50% by weight of the solids in the syrup of the neutralizing antacid, the neutralizing antacid being selected from the group consisting of aluminum salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mixtures thereof; and

c) applying the coating syrup to the cores and drying the syrup to produce a coating on the cores.

2. The method of claim 1 wherein the bulk sweetener is a polyol.

3. The method of claim 1 wherein the bulk sweetener is a sugar.
4. The method of claim 3 wherein the polyol is selected from the group consisting of sorbitol, xylitol, erythritol, maltitol, lactitol, hydrogenated isomaltulose and combinations thereof.
5. The method of claim 1 wherein the neutralizing antacid is selected from the group consisting of carbonate and hydroxide salts of magnesium, aluminum and bismuth.
6. The method of claim 1 wherein the antacid has a median particle size of between about 3 microns and about 75 microns.
7. The method of claim 1 wherein the antacid has a median particle size of between about 3 microns and about 15 microns.
8. The method of claim 1 wherein the coating syrup further comprises a binding agent.
9. The method of claim 8 wherein the binding agent is selected from the group consisting of gum arabic, gum talha, guar gum, karaya gum, locust bean gum, alginate-gums, xanthan gum, arabinogalactan, cellulose derivatives, vegetable gums, gelatin and mixtures thereof.
10. The method of claim 8 wherein the binding agent comprises at least about 2% of the coating syrup.
11. The method of claim 1 wherein the antacid comprises between about 30% and about 40% of the total solids in the coating syrup.
12. The method of claim 1 wherein the coated products contain 250 to 800 milligrams of antacid per piece.
13. The method of claim 1 wherein the antacid comprises between about 30% and about 40% of the coating.
14. The method of claim 1 wherein the coating further comprises a high-intensity sweetener.
15. The method of claim 14 wherein the high-intensity sweetener is selected from the group consisting of sucralose, aspartame, N-substituted APM derivatives, salts of acesulfame, alitame, saccharin and its salts, cyclamic acid and its salts, glycyrrhizin, dihydrochalcones, thaumatin, monellin and mixtures thereof.
16. The method of claim 1 wherein the bulk sweetener comprises maltitol.
17. The method of claim 1 wherein the coating is sugarless.
18. The method of claim 14 wherein the high-intensity sweetener is applied as part of a different coating syrup from the coating syrup containing the antacid.
19. The method of claim 14 wherein the high-intensity sweetener comprises acesulfame K.
20. The method of claim 1 wherein a powdered bulk sweetener is applied to the cores after application of the coating syrup.
21. The method of claim 1 wherein the coating further comprises an acid blocker.
22. The method of claim 21 wherein the acid blocker comprises a histamine  $H_2$  - receptor antagonist.
23. The method of claim 22 wherein the histamine  $H_2$  - receptor antagonist is selected from the group consisting of cimetidine, ranitidine and its active salt, famotidine, nizatidine and mixtures thereof.
24. The method of claim 22 wherein the histamine  $H_2$  - receptor antagonist comprises famotidine.
25. A chewing gum product made by the method of claim 1.
26. A method of making antacid coated chewing gum products comprising the steps of:
  - a) providing chewing gum cores;
  - b) providing a coating syrup comprising:
    - i) a bulk sweetener and
    - ii) a neutralizing antacid having a median particle size of at least about 3 microns and being suspended in the coating syrup, the coating syrup containing from about 25% to about 50% by weight of the solids in the syrup of the neutralizing antacid, the neutralizing antacid being selected from the group consisting of aluminum salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mixtures thereof;
  - c) providing a dry charge material comprising a bulk sweetener; and
  - d) applying the coating syrup and dry charge material to the chewing gum cores to produce a coating on the cores.
27. The method of claim 26 wherein the coating comprises about 30% to about 75% maltitol.
28. The method of claim 26 wherein multiple coats of coating syrup and dry charge material are applied to build up the coating.
29. The method of claim 26 wherein the dry charge material and coating syrup both include maltitol as the bulk sweetener.
30. A method of delivering an antacid to an individual that provides relief in the gastrointestinal tract comprising the steps of:
  - a) providing chewing gum cores;
  - b) providing a coating syrup comprising:
    - i) a bulk sweetener and
    - ii) a neutralizing antacid suspended in the coating syrup, the coating syrup containing from about 25% to about 50% by weight of the solids in the syrup of the neutralizing antacid, the neutralizing antacid being selected from the group consisting of aluminum salts, bismuth salts, magnesium salts, sodium bicarbonate, potassium bicarbonate, potassium citrate, sodium potassium tartrate, tricalcium phosphate and mixtures thereof;
  - c) applying the coating syrup to the cores and drying the syrup to produce a coating on the cores; and
  - d) chewing the antacid coated chewing gum product in the mouth and swallowing the coating, the coating dispersing and dissolving to provide an antacid in the gastrointestinal tract.
31. The method of claim 1 wherein the antacid is an aluminum salt selected from the group consisting of aluminum sodium carbonate hexitol complex; carbonic acid-aluminum magnesium complex; aluminum hydroxide; aluminum magnesium silicate; aluminum phosphate; aluminum hydroxide-aluminum carbonate gel; basic aluminum sucrose sulfate complex; dihydroxyaluminum aminoacetate; dihy

droxyaluminum sodium carbonate; aluminum magnesium hydroxide monohydrate and mixtures thereof.

32. The method of claim 1 wherein the antacid is a bismuth salt selected from the group consisting of bismuth aluminate, bismuth phosphate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate and mixtures thereof.

33. The method of claim 1 wherein the antacid is a magnesium salt selected from the group consisting of magnesium carbonate; magnesium hydroxide; magnesium oxide; magnesium peroxide; magnesium phosphate, tribasic; magnesium silicates; magnesium aluminosilicates and mixtures thereof.

\* \* \* \* \*





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## The Next Blockbuster Drugs

From cholesterol fighters to asthma relief, these treatments could earn Big Pharma \$170 billion



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By Mike Tarsala | 24/7 Wall St.

Jul 22, 2009 | Updated: 12:29 p.m. ET Jul 22, 2009

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Safety and efficacy data are critical to drug candidates. But what really makes a potential drug attractive is strong top-line data, a new biotech-based treatment, and a massive potential market.

With help from Thomson Reuters' SD Pharma database and our own backlog of coverage, BioHealthInvestor.com, a 247wallst.com website, sought to find the most promising biopharmaceutical candidate from both biotech and pharmaceutical companies in each of the top 10 most prevalent medical conditions in the U.S.

To do so, we reviewed data and Thomson Reuters revenue projections for 745 prescription drugs. We started by identifying the top sellers in each of the top 10 conditions, then looked at promising candidates that threaten to one day supplant the market leaders. All



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Keith Naughton

We have the technology, so why are our cars still so inefficient?

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of these challenger treatments can lead easily to a blockbuster drug status, meaning annual sales of \$1 billion or more.

Here are the top 10 medical conditions, sales estimates for the leading drugs, and the up-and-coming biotech-based candidates:

### 1. CHOLESTEROL FIGHTERS:

Exercise. Lose weight. Avoid trans fats. Sound familiar? Millions in the U.S. already have tried those things to some degree their bad cholesterol still is not at reasonable levels. It's why cholesterol-lowering agents are the No. 1 type of prescribed medication in the U.S., and are expected to generate \$27.4 billion in sales this year, according to Thomson Reuters SD Pharma estimates.

Cholesterol-lowering agents are arguably the top U.S. lifestyle drug. An American Journal of Medicine article in June suggested that Americans have worse health habits than they did 18 years ago. Waistlines are expanding. Physical activity has decreased, and so has healthy eating. It's why doctors are apt to prescribe cholesterol-lowering drugs such as statins to patients as young as their late-20s. The drugs have been shown to cut cholesterol, and thereby reducing the risk of heart disease.

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world's leading brands



\*Based on 2008 Amway sales

In the future, even patients with normal cholesterol levels may be prescribed statins. An American Heart Association study in November showed that AstraZeneca's statin Crestor dramatically cut deaths, heart attacks and strokes in patients that had fine cholesterol levels, but high levels of a heart disease-related protein.

There are about 34 million people in the U.S. that would benefit from taking statins to cut their heart attack and stroke risk, the AHA says. But that number could potentially increase by another 10 million if the new data were to be adopted into the association's guideline.

The class-leading drug is Lipitor from Pfizer Inc., with about 41 percent of the market, and expected sales of about \$11.2 billion this year. Other heavyweights include Crestor, with projected sales of \$4.9 billion, and Merck's cholesterol eating non-statin, Zetia, with projected sales of \$2.1 billion.

### The Potential Blockbusters:

The up-and-coming cholesterol-lowering candidate to watch is a potential biopharmaceutical from Aegerion Pharmaceuticals called Lomitapide. It is a small molecule drug that works to reduce blood levels of cholesterol and triglycerides by limiting the production of lipoproteins from the intestine and liver.

**Detroit & Economy: Can GM and Ford Survive?**



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Privately held Aegerion Pharma released interim Phase III data for Lomitapide in June. Among patients studied, Lomitapide reduced bad cholesterol by 44 percent. Interestingly enough, Aegerion entered into collaboration with Pfizer Inc. and the University of Pennsylvania for a cross-license relationship covering a range of patents related to the use of microsomal triglyceride transfer protein inhibitors.

## **2. INSULIN AND DIABETES TREATMENTS:**

The U.S. Centers for Disease Control says that \$116 billion was spent on treating diabetes in the U.S. in 2007. And because it's a disease where a quarter of the 23.6 million affected are unaware that they have it, sales of these treatments may soon climb under proposed health care reform plans.

For many who have it, diabetes requires insulin or other daily medications.

Expected 2009 spending on those drugs is \$23.3 billion, according to Thomson Reuters' SD Pharma data, second only to cholesterol-fighting drugs.

The vast majority of Americans diagnosed with the disease have Type 2 diabetes, a condition where insulin levels rise because the body fails to properly use it. Over time, the disease can cause malfunctions of the eyes, kidneys, nerves and heart. It's a main reason diabetes is the seventh-leading cause of death.

Daily medications are a fact of life for the majority of patients with Type 1 diabetes, which used to be called juvenile diabetes. And it is creating billions in profit for drug companies that treat patients with Type 2 diabetes, as well.

Leading diabetes drugs include several long-acting insulins. Once-weekly dosing is a huge opportunity, considering the daily needle-pricks required for many with both Type 1 and Type 2 diabetes. The best-seller is the Sanofi-Aventis drug Lantus, with expected revenue in 2009 of more than \$4 billion. Yet the current drug to beat for long-lasting insulin may be from Novo-Nordisk, following recent data that showed a potential link to cancer risk among Lantus patients.

### **The Potential Blockbusters:**

The true up-and-comer, however, may be an inhalable biopharmaceutical insulin candidate from MannKind Corp. called Afresia. It's true that inhalable insulin has been under development for a long time that has had issues from the start. But MannKind shares recently posted a new 52-week high on Afresia study data. In a late-stage study, the Valencia, Calif.-based company said Afresia's performance was shown to be comparable to injectable insulin.

Expectations are rising that MannKind may soon secure a worldwide marketing and development partner for Afresia, and that it likely will be an approved product by next spring.

One possible partner might be Pfizer Inc., which started switching its Exubera inhaled-insulin patients to MannKind's experimental product. The companies had been partners until Pfizer pulled Exubera from the market in 2007 after showing poor sales.

### 3. BLOOD PRESSURE

High blood pressure has become the norm for U.S. seniors; two-thirds of Americans age 60 or older have the condition. It's one of the most prevalent health plagues in the country, affecting men and women equally.

Overall, 29 percent of adults age 18 or older have hypertension, including about 7 percent of those who do not know they have the condition, according to the CDC. And 68 percent of those with the condition are taking medications to bring their BPs down. It's why spending on blood pressure meds is expected to top \$21.4 billion this year, according to Thomson Reuters SD Pharma data.

High blood pressure boosts the risk of heart attack, heart failure, stroke, and kidney disease. On the other hand, a common factor for those over 80, worldwide is normal or low blood pressure.

The CDC's facts and figures do not include an additional 28 percent of the U.S. adult population that has pre-hypertension, a diagnoses that raises the chances of a person developing high blood pressure.

The top-selling blood pressure drug is Novartis AG's Diovan. It is expected to post 2009 sales of about \$5.9 billion, according to Thomson Reuters data. But that number could fall dramatically when the pill's patent expires in 2012. The other big high-blood pressure treatment is Merck's drug Cozaar, with expected sales this year of about \$4.4 billion. Its patent is set to expire in 2010.

#### The Potential Blockbusters:

Although some concerns have been raised about its side effects, especially at high doses, the up-and-coming candidate to watch for high blood pressure is a biopharmaceutical from Gilead Sciences Inc. called Darusentan.

In May, the company announced data from one of its two Phase III clinical trials of the candidate in patients with resistant hypertension. The drug showed significant improvements in both systolic and diastolic blood pressures vs. placebo. Provided the second Phase III study backs up the efficacy data and raises no new safety concerns, the drug could receive FDA approval as early as 2011.

### 4. IMMUNE SYSTEM BOOSTERS/SUPPRESSANTS

One giant category of drugs that covers everything from vaccines to anti-rejection transplant drugs is called immunomodulators — drugs that either stimulate or suppress the body's immune system.

A growing number of the immunomodulators in development are biopharmaceutical compounds, such as recombinant proteins and peptides, monoclonal antibodies, and vaccines that are being used to fight multiple types of conditions and diseases, including some types of cancer.

The biggest drugs in the category are designed at least partially as a treatment for arthritis, the leading cause of disability in the U.S., and one that affects more than

half of seniors. The CDC projects that the number of people age 65 or older who have arthritis or chronic joint symptoms will nearly double from 21.4 million in 2001 to 41.4 million in 2030, as more people are living longer.

About \$20.7 billion is expected to be spent on immune system modulators in 2009, a number that is expected to grow as the number of treatments that work with the body's immune system increases.

One of the top immune system suppressants — and the top-selling immunomodulator overall — is the Abbott Laboratories Inc. drug Humira, which works to shut down the body's inflammatory response for patients with arthritis and Crohn's disease. It was created using a particular type of human immune cell, which was a clone of a single parent cell. Popular competing drugs are Johnson & Johnson's Remicade, with expected sales of about \$4.3 billion this year, and Amgen Inc. and Wyeth's Enbrel, with expected sales of about \$3.4 billion.

#### **The Potential Blockbusters:**

The company to watch in immunomodulation is Array Biopharma Inc., which has five total MEK inhibitor candidates, and two that could eventually find markets in both cancer and rheumatoid arthritis — ARRY-162 and ARRY-300.

The furthest along of the two early candidates is ARRY-162, which is now in a Phase II trial in 200 patients with rheumatoid arthritis. So far, the candidate has been well tolerated and with no patients that discontinued the study due to an adverse event. The efficacy data in that trial is expected to be released in September, an event that's a likely catalyst for the company's stock.

Meanwhile, ARRY has a Phase I of ARRY-300 in rheumatoid arthritis under way, and in mid-July filed an investigational new drug application for ARRY-162, in anticipation of a Phase I cancer trial.

#### **5. ASTHMA**

One type of trauma that will get you in to see an emergency room doctor than most any other is an asthma attack. The reason is simple: breathing is the most critical necessity of life.

The CDC says that about 7.3 percent of adults and 9.1 percent of children have asthma, the most common respiratory disease other than sinusitis. In 2004, the most recent CDC data available, some 4.2 percent of people in the U.S. had at least one asthma attack. The disease leads to nearly 2 million emergency room visits a year, and tens of thousands of missed days of school and work. It's the reason that about \$20.2 billion will be spent on asthma medications in the U.S. this year, according to Thomson Reuters SD Pharma.

The most commonly prescribed asthma drug is GlaxoSmithKline's Advair, with projected sales of \$7.4 billion. It works to boost lung function by opening restricted airways and tamping down inflammation. Another popular drug is Merck & Co's Singular, which helps to block genetic signals that trigger airway

constriction.

#### **The Potential Blockbusters:**

Perhaps the asthma drug to watch is fluticasone furoate, developed by GlaxoSmithKline, in partnership with Theravance Inc. The two companies are working on a potential follow-up to Advair.

Glaxo and Theravance announced results of three separate Phase IIb studies of the candidate across a range of eight doses in more than 1,800 patients. Fluticasone furoate was effective in all but the lowest dose tested. Only the highest dose showed a statistically significant boost in a side effect typical of its type of inhaled steroid. A Phase III trial could start early next year.

#### **6. ANTIPSYCHOTICS**

Mental illnesses might not be top of mind when it comes to a list of top medical conditions. Yet one in four adults in the U.S. has a diagnosable mental disorder in a given year. About 6 percent have a serious mental illness, according to the National Institute of Mental Health.

One of the top mental illnesses being treated with prescription drugs is bipolar disorder, a disease that can cause extreme mood swings, from infrequent manic highs to more common depressive lows. It is the leading mental health diagnosis that contributes to lost work productivity. The median age for the disease's onset is 25 years, which is why many with bipolar disorder are on antipsychotic medications for most of their adult lives.

Nearly \$16.7 billion will be spent in the U.S. this year on medications to treat mental illnesses including bipolar disorder, according to Thomson Reuters SD Pharma. The top drug in the category is the bipolar disorder drug Seroquel, made by AstraZeneca plc, with expected sales of \$5.4 billion, accounting for about a third of all antipsychotic drug sales. The No. 2 drug in the category is Eli Lilly & Co.'s Zyprexa, for treating bipolar disorder and schizophrenia. Expected sales this year are \$4.6 billion.

There are other potential markets for drug manufacturers, and for some drugs already in the category. Mental illnesses that may require antipsychotics include major depressive disorder, anxiety disorder, panic disorder, and obsessive-compulsive disorder. Many affected by mental illness have multiple disorders and phobias.

#### **The Potential Blockbusters:**

There are a number of seemingly promising antipsychotic drug candidates, but one at the top of the list is paliperidone palmitate for treating schizophrenia. The drug is being developed by Johnson & Johnson, with NanoCrystal technology from Elan Corp.

The FDA in August 2008 asked for more data on the drug before allowing it on to the U.S. market. But it has not asked for additional trials. The drug was effective in

studies, with only 10 to 15 percent of patients relapsing, vs. 40 percent in the placebo group.

The main advantage of paliperidone palmitate could be in its delivery. It's an injection taken once monthly, which in theory could make it much easier for schizophrenics to stay on their medications.

## 7. HEARTBURN DRUGS

Heartburn, or acid reflux, is very common, very uncomfortable, and a condition that can lead to more serious medical conditions if left untreated. It's why \$13.1 billion will be spent this year on a particular class of prescription acid reflux medications, according to Thomson Reuters SD Pharma data.

Roughly 60 million adults report suffering from acid reflux at least once a month, according to the American College of Gastroenterology. And about 20 percent of those people develop a more serious condition associated with immune system weakness and a higher esophagus cancer risk.

The most common prescription treatment for acid reflux is a class of drugs called proton pump inhibitors. They work to block the production of stomach acid that causes heartburn. Unlike fast-acting medications like over-the-counter antacids, proton pump inhibitors take much longer to work, but they offer long-lasting relief.







The top prescription heartburn treatment by far is AstraZeneca plc's "purple pill" Nexium, with 2009 expected revenue of about \$5.6 billion, and more than 40 percent market share. The No. 2 is Takeda Pharmaceutical's Prevacid, with roughly 17 percent share, and projected revenue of about \$2.2 billion.

### The Potential Blockbusters:

There appear to be few significant near-term challengers on the horizon to the Nexium; the drug does not start coming off patent until 2015. But one company with a candidate that could be a contender is Orexo AB, with its OX17 proton pump inhibitor. It is being developed for the treatment of gastro esophageal reflux disease, the most serious form of acid reflux. It combines two substances in an effort to provide both long-lasting and fast-acting heartburn relief.

In a Phase II trial last year, OX17 quickly proved effective in working fast and continuing to work to reduce stomach acid. Earlier this year, Orexo signed an exclusive development deal with a yet-to-be-named partner. The company expects to announce a licensing deal for its OX17 program this year, as well.

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Posted By: MichaelX @ 08/05/2009 10:48:22 AM

Reply Report

Can you say \$ that's all that it's about.  
Whether you are cured, or better off, is no matter to these "drug lords" who operate with impunity. STOP USING PRESCRIPTION DRUGS! All you need is Marijuana, clean water, and a healthy diet to survive. Most "ailments" are from the very "concoctions" that these immoral people foist upon the public. Put them out of business! Do not but their products unless they use qualified, known, usefull bio-metric substances. HEMP, yes, "pot" is the most usefull bio-mass on this planet, and we need to demand that it's various permutations be used. Big Pham, be warned, and be advised, use it , or lose it.

Posted By: DannyHaszard @ 07/22/2009 6:31:54 PM

Reply Report

Eli Lilly Zyprexa can cause diabetes

I took Zyprexa a powerful Lilly schizophrenic drug for 4 years it was prescribed to me off-label for post traumatic stress disorder was ineffective costly and gave me diabetes. This is a powerful drug that can damage a young person physiologically for life.

Please take with caution and learn as much as you can about side effects.

Eli Lilly's #1 cash cow Zyprexa drug sale \$38 billion dollars so far, has a ten times greater risk of causing type 2 diabetes over the non-user of Zyprexa.

So, here we have a conflict of interest that this same company also is a big profiteer of diabetes treatment.

#### WARNING-

If a drug (Zyprexa) lists anything about the pancreas among the side effects, it probably means it can cause diabetes.

Unlike your liver, the pancreas does not regenerate itself. If it gets damaged, diabetes is very likely.

Zyprexa is glorified Thorazine at ten times the price

Daniel Haszard <http://www.zyprexa-victims.com>

Posted By: DannyHaszard @ 07/22/2009 3:30:40 PM

Reply Report

Great news that Eli Lilly is posting profit, as a Zyprexa damage claimant who got diabetes from it I know that Lilly can afford to pay me my settlement.







Daniel Haszard <http://www.zyprexa-victims.com>[View All Comments »](#)

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